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THE EFFECT OF PENICILLIN IN EXPERIMENTAL INTESTINAL OBSTRUCTION

Preliminary Report on Closed Loop Studies

W. HENRY HARPER, M.D.,[1] AND ALEXANDER BLAIN, III, M.D.

From the Departments of Surgery and Pathology of the Johns Hopkins Medical School and the Johns Hopkins Hospital

It has long been recognized that patients with intestinal obstruction will die with a rather characteristic symptomatology which has been described as due to a "toxemia" unless the intestinal contents above the site of the obstruction can be removed. Replacement of water and chloride lost in vomiting will often lengthen the number of days these patients can live, but unless the material above the obstruction is removed by surgical drainage or intubation, the patients die. An enormous amount of investigation has been carried out to determine whether or not a toxin is formed in the obstructed loop, and if it exists, what factors are involved in its absorption from the obstructed intestine. Many careful observers have concluded that a toxin is elaborated in intestinal obstruction (10, 11, 23, 28), and that its chief route of absorption is through the distended intestinal wall (15, 27, 29). These conclusions, however, have not been universally accepted by any means, and with the important contributions and success attending electrolyte and water replacement therapy (20, 21, 13, 14, 6), etc., and relief of distension by intubation (1, 19, 31), etc., the question of the existence of a "toxin" has been largely overshadowed.

No attempt to review the exhaustive literature on this subject will be made. Several review articles have been published. One of the most valuable and complete of these is by Cooper (7).

To give some indication of the unsettled status of this problem, the following quotations are taken from leading text-books in physiology, pathology, and surgery.

Best and Taylor, in the "Physiological Basis of Medical Practice,"

[1] William Stewart Halsted Fellow in Surgery.

The bacteriological studies were performed by Miss Carolina Quintero of the Department of Bacteriology.

1944 (2), state that "A bacterial theory in one or the other of its modifications has had its adherents. The "toxin" of the Welch bacillus has been suspected by some, but little support has been given by recent work to the belief that this or any other bacterial "toxin" is responsible for the symptoms (of intestinal obstruction)." They also state that "It is impossible to consider seriously any bacterial theory of intestinal obstruction for such theories ignore the fact that the symptoms diminish in intensity and the survival time is lengthened the lower in the intestinal tract the obstruction is produced."

William Boyd, in his "Textbook of Pathology" (1944) (4), states that "The cause of fatal toxic symptoms, most marked in the high obstruction, has long been a subject of controversy. Absorption of highly toxic protein products in the obstructed loop may play some part (Whipple). Loss of chlorides, due to continuous vomiting, has been considered of such importance that sodium chloride has been administered as a form of treatment (Haden and Orr), but without any significant impression on the high mortality. It appears probable that the most important factor is distension of the bowel and that shock plays a leading part in severe and fatal cases."

John Homans, in his "Textbook of Surgery" (1940) (17), says that "On the whole the toxic material which has seemed to be formed in a strangulated loop of gut has about the same vague status as that of crushed tissues and burns."

Our purpose in conducting the studies to be described in this report was to reinvestigate the rôle of bacteria in producing death in dogs having isolated obstructed jejunal loops. To study the importance of bacteria or the products of bacterial growth, we used potent antibacterial agents, especially penicillin, having no known important chemical or other action on the body. These antibacterial agents or others like them were not available to the earlier workers in this field. Although we started with sulfasuccidine, it was soon discarded, because it coated the closed loop mucosa with an insoluble paste, thus interfering with absorption. Only the studies in which penicillin was used will be reported here.

In the study of the question of the relation of "toxemia" to intestinal obstruction, it has been common practice to use what is termed the "isolated obstructed loop" procedure. Briefly, this consists of resect-

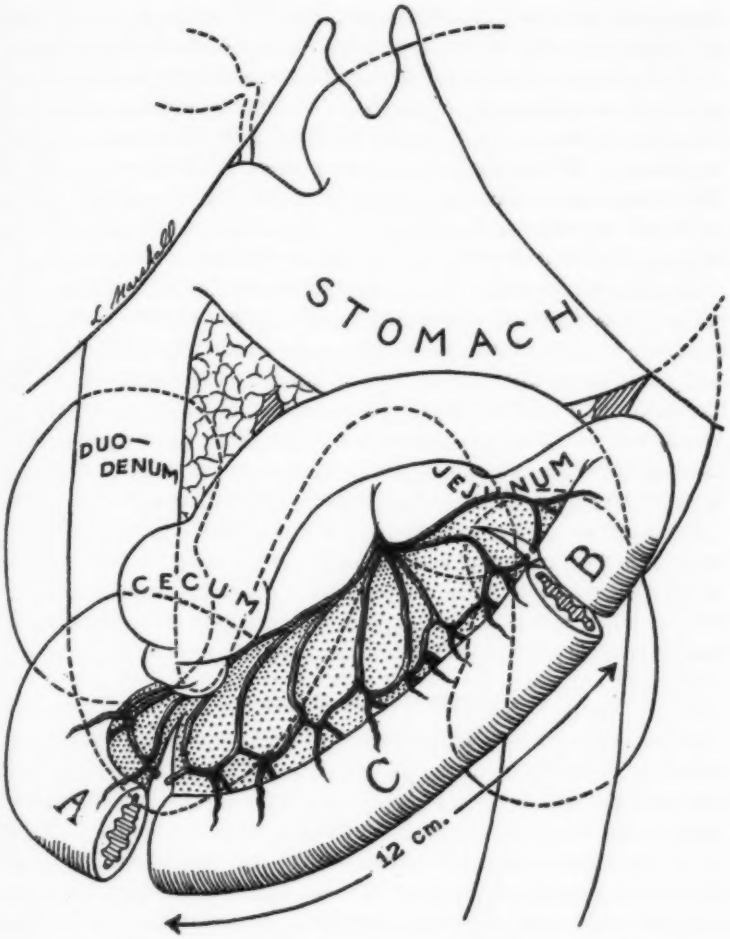

FIG. 1. DIAGRAM SHOWING LOCATION OF LOOPS REMOVED IN THESE EXPERIMENTS

The jejunum is cut at A and B and the continuity of the bowel is restored by an end-to-end anastomosis. The ends of segment C are turned in, forming an isolated obstructed loop with an intact blood supply.

ing a length of bowel (in our studies, twelve centimeters of jejunum) and closing its ends with sutures after the intestinal tract continuity has been restored by an end-to-end anastomosis of the proximal and distal ends of the unresected bowel. The free isolated obstructed segment has an intact blood supply by way of its mesentery. In the experience of all investigators, only very rarely will a dog survive more than several days under these conditions (10, 28). It may be well to point out the value of the isolated obstructed loop for a study of this nature. In the first place, the factors of the presence of pancreatic juice, bile, and decomposed food substances are eliminated. Also, loss of electrolytes and water by vomiting is largely obviated (7, 18) because dogs with isolated obstructed loops usually vomit only terminally and rarely lose more than two to four hundred cubic centimeters. The blood chemistry of these dogs remains nearly normal or normal (7, 8). The factors which remain and can be studied are: (a) the presence of bacteria, (b) stasis and, subsequently, when escape of fluid into the loop exceeds absorption of fluid from the loop, (c) the factor of distension.

Inasmuch as we have studied the action of bacteria and have not studied the factors of fluid loss and electrolyte imbalance in intestinal obstruction, no attempt to compare the relative importance of these factors will be made. Clinically the relationship of these factors certainly varies, depending on the level and type of obstruction.

EXPERIMENTAL METHODS

All dogs in this study were operated on under intravenous nembutal anesthesia. A portion of the jejunum about twelve centimeters long was resected and its blood supply was left intact. An end-to-end anastomosis was then used to restore the intestinal continuity (see Fig. 1). Five cubic centimeters of sterile saline was then washed through the loop and placed in a culture tube for bacteriological study. The loop was then washed thoroughly with three hundred cubic centimeters of sterile saline to remove all gross intraluminal material. The ends of the loop were inverted by the Parker Kerr technique and the abdomen closed. The operative time was usually about fifty-five minutes. Picrotoxin was used when necessary for the relief of respiratory depression. This procedure was carried out in all dogs reported in this series.

Fifteen dogs received no penicillin therapy and were used as controls.

Fifteen dogs received 50,000 units of penicillin in four cubic centimeters of saline in the isolated loop before it was closed. Five additional dogs were given large doses of penicillin intramuscularly (in one case, intravenously) starting at time of operation. The doses for each dog treated parenterally were: 100,000 units every two hours for the first twenty hours, 50,000 units every two hours for the next twenty hours, and 50,000 units every four hours during forty additional hours (a total of 2,000,000 units in eighty hours for each dog). Food was withheld one day pre-operatively and three days post-operatively. Water was withheld until twenty-four hours post-operatively. All dogs receiving penicillin had cultures taken of their loops at the end of thirty days or when they died. All dogs that died had an autopsy done as soon as possible after death. The obstructed isolated loop and the anastomosis were removed at death, photographed, cultured and then placed in formalin along with sections of the major organs. The peritoneal contents and the heart blood were also cultured. Microscopic sections of tissues removed at autopsy were made and bacterial stains were done on all sections of the intestine.

RESULTS

1. Control dogs. Thirteen of the fifteen control dogs with isolated intestinal loops died within three and a half days. One died at four and a half days and one at six and a half days (Fig. 2). The symptomatology was the same in all animals. The day following the operation the dogs would be up and walking and would bark, scratch and wag their tails. The abdomen would be warm, but soft. The second post-operative day the dogs would appear to be a little quieter and would stretch often. The loop could be easily palpated at this time and in every case it was very firm and distended. About six hours before death the abdominal musculature would become rigid and retching would occur intermittently. A total of somewhat under four hundred cubic centimeters of vomitus would be lost before death. The hind legs would become weak, then the dog would lie down, stretch his limbs and later only his head would move about, and finally, just before death, only his eyes would move. The respirations would increase to about sixty per minute and the pulse rate would usually exceed two hundred before death. The dog's eyes would close, the respirations

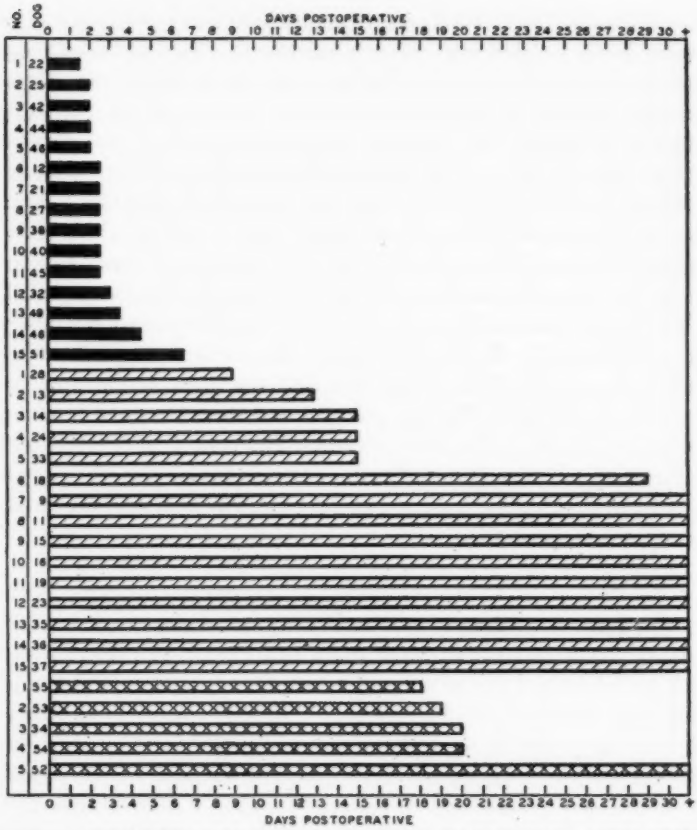

FIG. 2. DIAGRAM SHOWING RELATIVE SURVIVAL TIMES OF DOGS WITH ISOLATED OBSTRUCTED LOOPS NOT TREATED WITH PENICILLIN AS CONTRASTED WITH THE SURVIVAL TIMES OF DOGS WITH ISOLATED OBSTRUCTED LOOPS TREATED WITH PENICILLIN.

cease and later the heart would stop. At autopsy all control dogs had a distended and discolored loop. In six dogs the loop was not grossly perforated. (Fig. 3) In nine dogs the loop was perforated in one or more places. (Figs. 5 and 6) All loops had a red swollen mucosa with gross ulceration along the antimesenteric border (Figs. 4 and 6). These loops were filled with a foul-smelling, red hemorrhagic material such as is often seen above the site of obstruction in untreated human cases. All controls had about twenty-five to a hundred cubic centimeters of blood-tinged fluid in the abdominal cavity, whether or not the loop was perforated. All control loops showed microscopic evidence of ulceration, necrosis of the intestinal wall, and haemorrhage and infection of the wall. (Fig. 13) This process was in every case more extensive along the antimesenteric border (Figs. 4 and 6). Bacterial stains revealed the presence of many types of bacteria, both Gram positive and Gram negative in the acutely inflamed areas. (Fig. 14) No thrombosed blood vessels could be found. Thus, all that can be said is that at the time of death there was acute ulceration, bacterial invasion and hemorrhage of the intestinal wall, in all of the isolated loops in the untreated control dogs.

2. Dogs receiving fifty thousand units of penicillin in the isolated loop at the time of operation.

Of the fifteen dogs that received fifty thousand units of penicillin in the isolated loop at operation, sixty per cent were protected for over a month, at which time they were used for further experimental studies; ninety-three per cent lived thirteen days or longer; and a hundred per cent lived nine days or longer (Fig. 2). The first day after operation they appeared almost the same as before operation, and some seemed normal until the third day, but all had tense, easily palpable, distended loops from the second through the fourth days (Figs. 7 and 9). From the third to fourth days almost all the dogs retched and vomited and some even appeared as though they were going to die. By the end of the fifth or sixth day the loops were noticeably less tense on palpation and most of the dogs began to eat for the first time and appeared to be convalescing. Following this the dogs were well until, in the case of the six that died, about four to six hours before death. They would vomit several times, the abdominal musculature would become rigid and they would have a terminal course similar to that of the control dogs. Dog

FIGS. 3–4

no. 13 died in thirteen days and was found to have a normal loop. This dog failed to eat following operation and the remainder of his autopsy findings revealed nothing but extreme malnutrition and dehydration. The remainder of the five penicillin treated dogs that died showed distended loops with infection and ulceration on the antimesenteric border. However, they also had small areas of ulceration further away from the antimesenteric side. The mucosa for the most part was not hemorrhagic or swollen. We have no explanation for the recurrence of the distension after it had once been relieved. The loop contents were reddish-brown, foul smelling, and very similar to the control loop contents. In all dogs in which penicillin was placed in the loop and that subsequently died, twenty-five to a hundred cubic centimeters of blood-tinged fluid was found in the abdominal cavity. By observing the loops removed at twenty-four, forty-eight (Fig. 7), seventy-eight and ninety-six hours (Fig. 9) for penicillin titration studies, it was confirmed, as had been suspected by extra-abdominal palpation, that even in the cases of dogs that survived thirty days, the loops became tense and distended from the second to fourth days. After this the loops diminished in size so that by the time of the second operation (thirty days after the first operation) they were healthy in appearance and only slightly larger than when they were originally constructed (Figs. 11 and 12). They were not tense and were partly collapsed. The contents varied from a cloudy, thin mucus, with a gray or brown sediment, to a thick, clay-colored, or dark brown, or greenish paste.

The microscopic sections of the isolated loops of the penicillin treated dogs that died showed changes quite like those of the untreated con-

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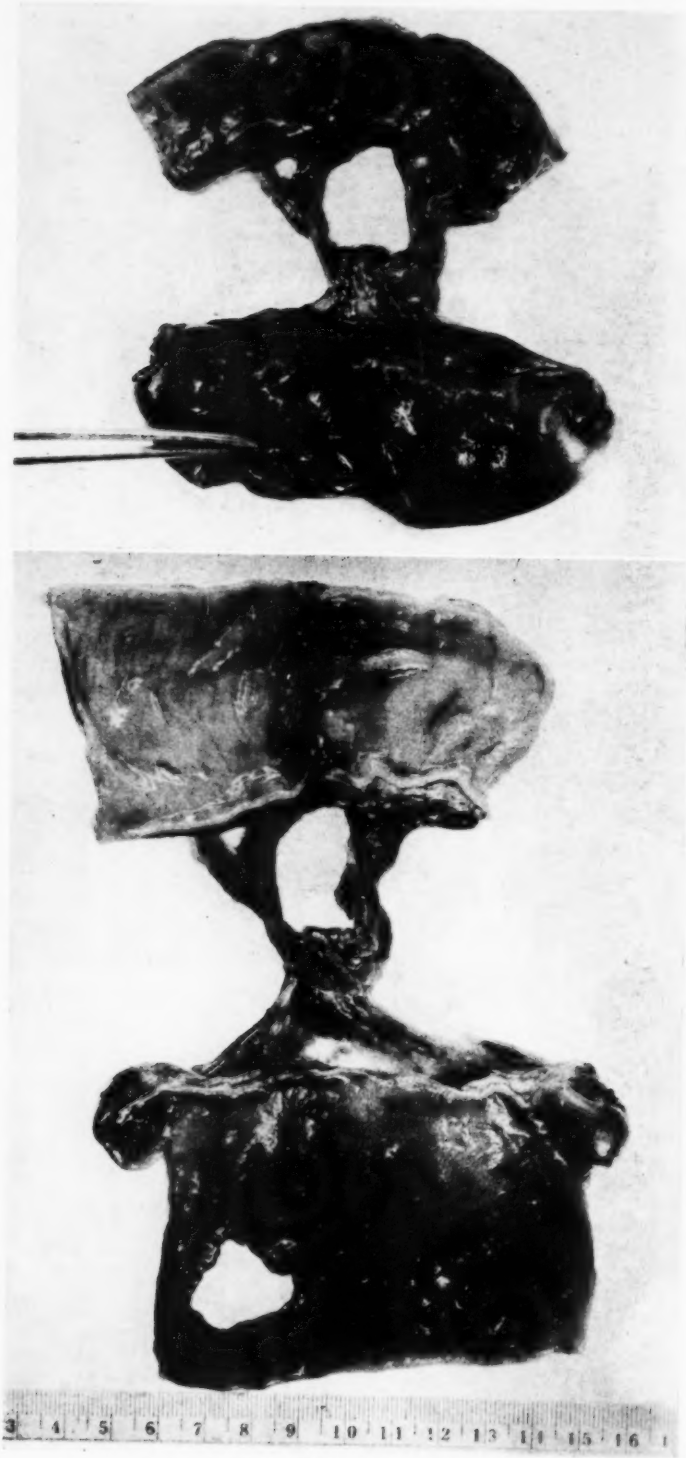
EXPLANATION OF ILLUSTRATIONS

(Photographs by Miss Elizabeth Cone and Miss Ruth Cordish, Department of Art as applied to Medicine, Photographic Division. Microphotographs by Mr. Chester Reather, Carnegie Institute of Washington.)

FIG. 3. Loop of control dog 21 (died 2¼ days), showing distension, but no gross perforation.

FIG. 4. Loop of control dog 21 opened showing hemorrhage and ulceration on antimesenteric border. Opened jejunum showing very little inverted tissue at anastomosis.



FIGS. 5–6

trols. The sections of the penicillin treated dogs that survived, and those of the penicillin treated dogs that were killed at intervals up to ninety-six hours, revealed no evidence of inflammation or bacterial invasion (Figs. 15 and 16). They were perfectly normal with the exception that there were small areas of petechial hemorrhages in the mucosa and intestinal wall of the loops removed at the time of greatest distension (Fig. 8).

3. Dogs with isolated loops treated intravenously or intramuscularly with penicillin.

Four dogs with closed jejunal loops were treated solely by the admiistration of penicillin intramuscularly. One dog was treated with penicillin intravenously for twenty-four hours and intramuscularly thereafter. These dogs were given one hundred thousand units every two hours for ten doses, fifty thousand units every two hours for the next ten doses and fifty thousand units every four hours for the last ten doses. This made a total of two million units given within a period of eighty hours for each dog. In general they followed the same post-operative course as that of the fifteen dogs into whose closed loops penicillin was placed at the time of operation (Fig. 2). On the second, third and fourth post-operative days large, tense, distended loops could be easily palpated through the abdominal wall. After the fourth day the loops became gradually less distended and less palpable.

We did not palpate the loops after the tenth day, however when four of these dogs died on the eighteenth, nineteenth and twentieth (two dogs) days respectively they all had large loops. Two were perforated and two were not. The fifth dog is still living.

4. Penicillin titration series. In view of the beneficial effects of penicillin enclosed in jejunal loops on the post-operative course of dogs, we were curious about the length of time that penicillin would remain in the loops in detectable quantities. Therefore, closed jejunal loops

FIG. 5. Loop of control dog 40 (died 2½ days), showing discoloration, perforation and collapse. Jejunal anastomosis above.

FIG. 6. Loop of control dog 40 opened, showing hemorrhage and ulceration along antimesenteric border with two perforations. Opened jejunum showing very little inverted tissue at anastomosis.

FIGS. 7–8

containing fifty thousand units were constructed in five dogs. These dogs were re-opened after an interval of twenty-four, forty-eight (two dogs), seventy-eight and ninety-six hours respectively. The contents were collected and were subjected to titration against a known strain of *Staphylococcus aureus*[2]. In the twenty-four hour specimen there were six hundred and forty units of penicillin per cubic centimeter of loop content. In neither of the two forty-eight specimens or in the ninety-six hour specimen was any penicillin detected. In the seventy-eight hour specimen there were still eight units of penicillin per cubic centimeter in the loop content.

In addition, penicillin titrations were carried out on the loop contents of four dogs, nine, fifteen and thirty days (two dogs) after fifty thousand units of penicillin had been placed in the isolated loop. No penicillin was detected in any of these loops. From these incomplete studies it appears that while penicillin can remain in the loop for at least twenty-four hours, it is usually not present in detectable amounts at the end of forty-eight hours, or thereafter.

In view of the efficacy of parenterally administered penicillin, it will be interesting to determine how much penicillin finds its way into an isolated loop following parenteral administration.

5. *Bacteriological studies.* At each operation in all these experiments the loop contents were cultured. At autopsy the loop contents, the peritoneal contents, and the heart blood were routinely cultured. This represents a total of over two hundred cultures. In each culture each organism was isolated and identified by the standard procedures used in this hospital. *Escherichia coli*, *Clostridium welchii*, Gamma *Streptococcus*, and *Staphylococcus aureus* were the organisms most frequently found in the loop at the time of the first operation. At autopsy these organisms were present in the loop, in the peritoneal

[2] All penicillin titrations were carried out by James W. Johnson of The Biological Division of the Medical Clinic.

FIG. 7. Loop of penicillin treated dog 41, removed forty-eight hours post operatively, showing distension.

FIG. 8. Loop of penicillin treated dog 41, opened, showing relatively normal looking mucosa with scattered petechial hemorrhages.

FIGS. 9–10

fluid and in sixty per cent of the heart blood cultures in the control dogs. It was found, while running the penicillin titration series, that as long as penicillin persisted in detectable concentrations, the cultures from the loops were reported as sterile. However, smears of the same material showed the presence of bacteria. As soon as the penicillin could be no longer detected in the loop content, the same organisms, in general, that were present at the time of the first operation, would begin to grow out. By the end of thirty days when the second operation was performed, a profuse growth of these same organisms was demonstrated in smears, in broth and on plates. Occasionally one organism would overgrow the rest and a pure culture would be found.

DISCUSSION

In this paper we use the word "toxemia" to designate the "toxic" symptoms that occur in intestinal obstruction independently of the symptoms arising as a result of the loss of electrolytes and water, and which can lead to death. The cause of this "toxemia" has long been a matter of dispute. Among other suggestions it has been attributed to an abnormal secretion of the mucosa of the distended loop (34), to bacterial action (9, 10, 24, 35), to break-down products of protein metabolism (33), to gastric content (26), to pancreatic juice (30), to bile (3), and to distension of the obstruction loop (5, 16, 32). The present experiments show that bacteria or their products are the cause of death in dogs with isolated obstructed loops. Foremost among the early proponents of this belief were Davis and Stone (9), Dragstedt (10) and Murphy and Brooks (23). The studies of Dragstedt are particularly important in this connection.

Those who have argued against the importance of bacteria in intestinal obstruction have asked why it is that the higher the site of intestinal obstruction, the faster death ensues, and yet fewer bacteria are present normally in the upper intestinal tract (2, 7). It must be remembered, however, that no matter where the obstruction occurs a

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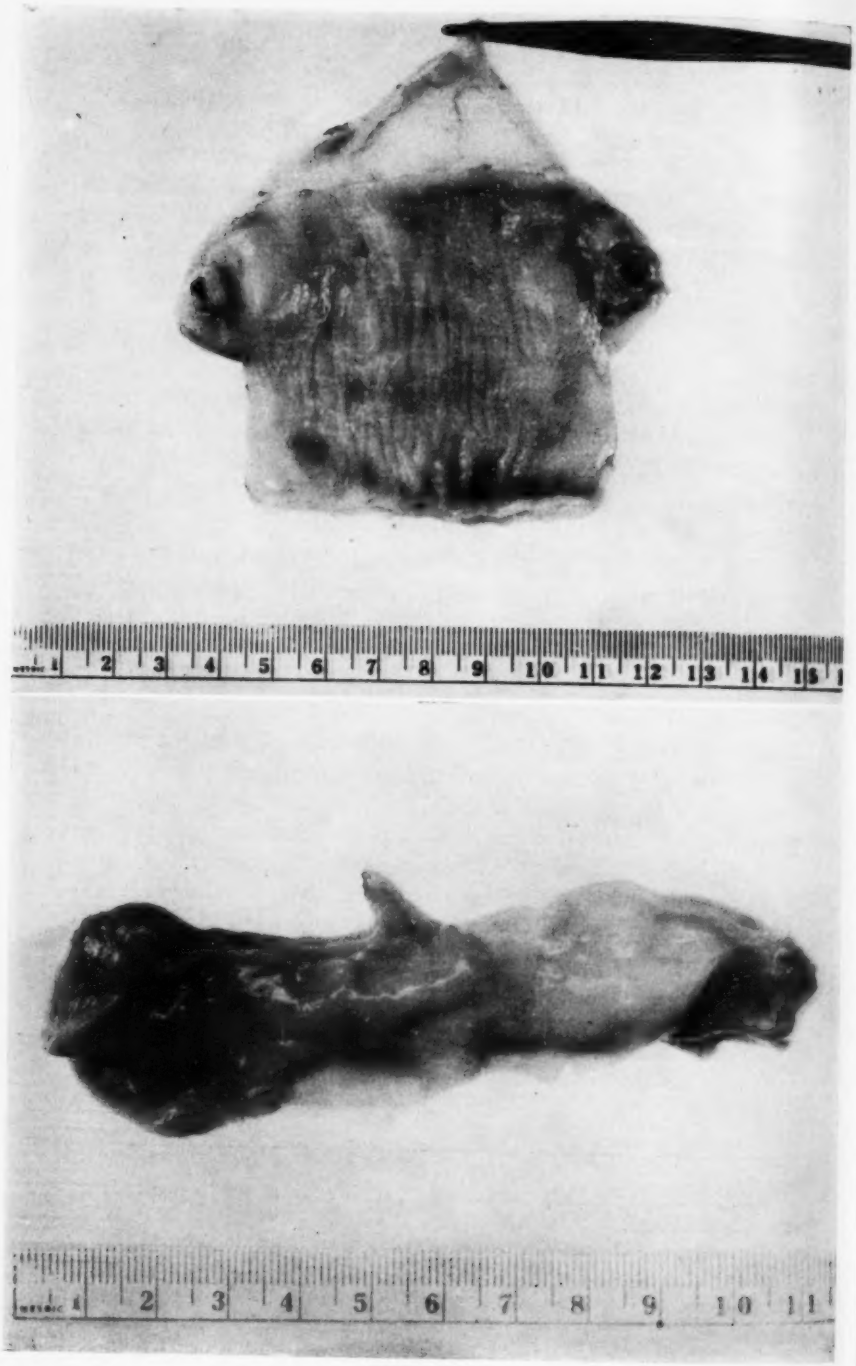
FIG. 9. Loop of penicillin treated dog 39, removed four days post-operatively, showing distension.

FIG. 10. Loop of penicillin treated dog 39, opened, showing normal looking mucosa.



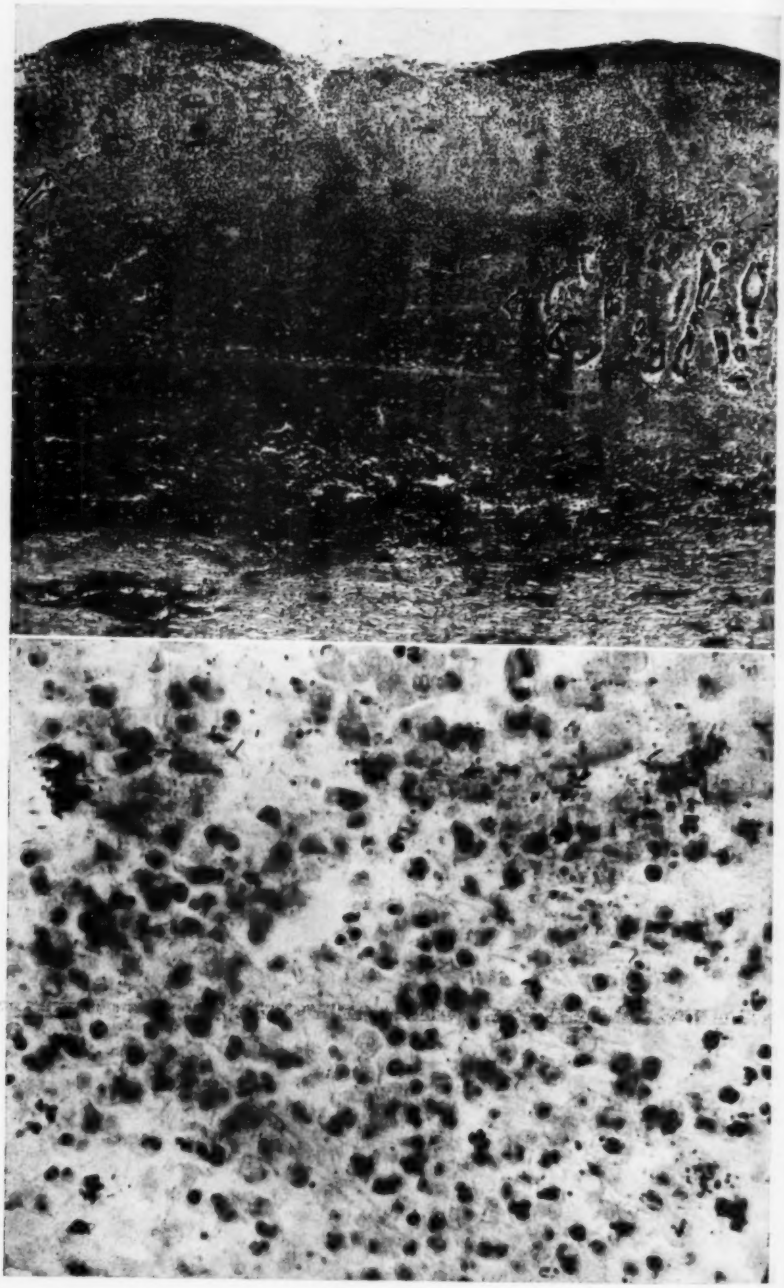
FIGS. 11–12

rapid and profuse bacterial growth will develop above its site. A question that may now be raised is, "Why is the course of high obstruction more rapidly fatal than low obstruction, if profuse bacterial growths are present in both cases?" We believe that this is due to the fact that the higher the site of obstruction, the more rapid is the accumulation of fluid and the more rapid the distension.

Morton and Sullivan (22) created intestinal closed loops ten cubic centimeters in length at different intestinal levels and placed them under the skin so they could be aspirated every twenty-four hours. The relative amounts of fluid at the different intestinal levels were then measured. In duodenal loops eleven cubic centimeters of fluid accumulated in twenty-four hours and thirty-six cubic centimeters in forty-eight hours. In low ileal loops only one cubic centimeter accumulated in seventy-two hours. The intraluminal pressure was found to be seven times as great in the duodenal as in the ileal loops after seventy-two hours. The contents of the high jejunal loops in our series were fifteen cubic centimeters in twenty-four hours and an average of forty cubic centimeters in forty-eight hours. We feel that we can say that infection of the intestinal tract by the normal intestinal flora will not occur without distension (or damaged tissue), because we have found that whether the dogs were treated with penicillin or not, there was a critical period during the second to fourth days in which all of the loops became tense and distended (Figs. 7 and 9). The intestinal wall can be protected from infection during this period by penicillin. Following this period the distension regresses, the penicillin disappears from the loop and the same bacteria that were present originally slowly regrow so that at the end of a month large growths of the same bacteria are present. However, because the distension is no longer present, there is no infection of the intestinal wall (Figs. 11 and 12). When intubation and suction are used to relieve intestinal obstruction, both of these factors (distension and bacterial overgrowth) are obviated. In high obstruction it seems probable that pancreatic juice also plays an important rôle in producing damage to the intestinal mucosa in the presence of distension. We are studying this phase of the problem at present.

FIG. 11. Loop of penicillin treated dog 35, removed one month post-operatively, opened, showing normal looking mucosa.

FIG. 12. Loop of penicillin treated dog 11, removed one month after operation, opened, showing normal looking mucosa.



FIGS. 13–14

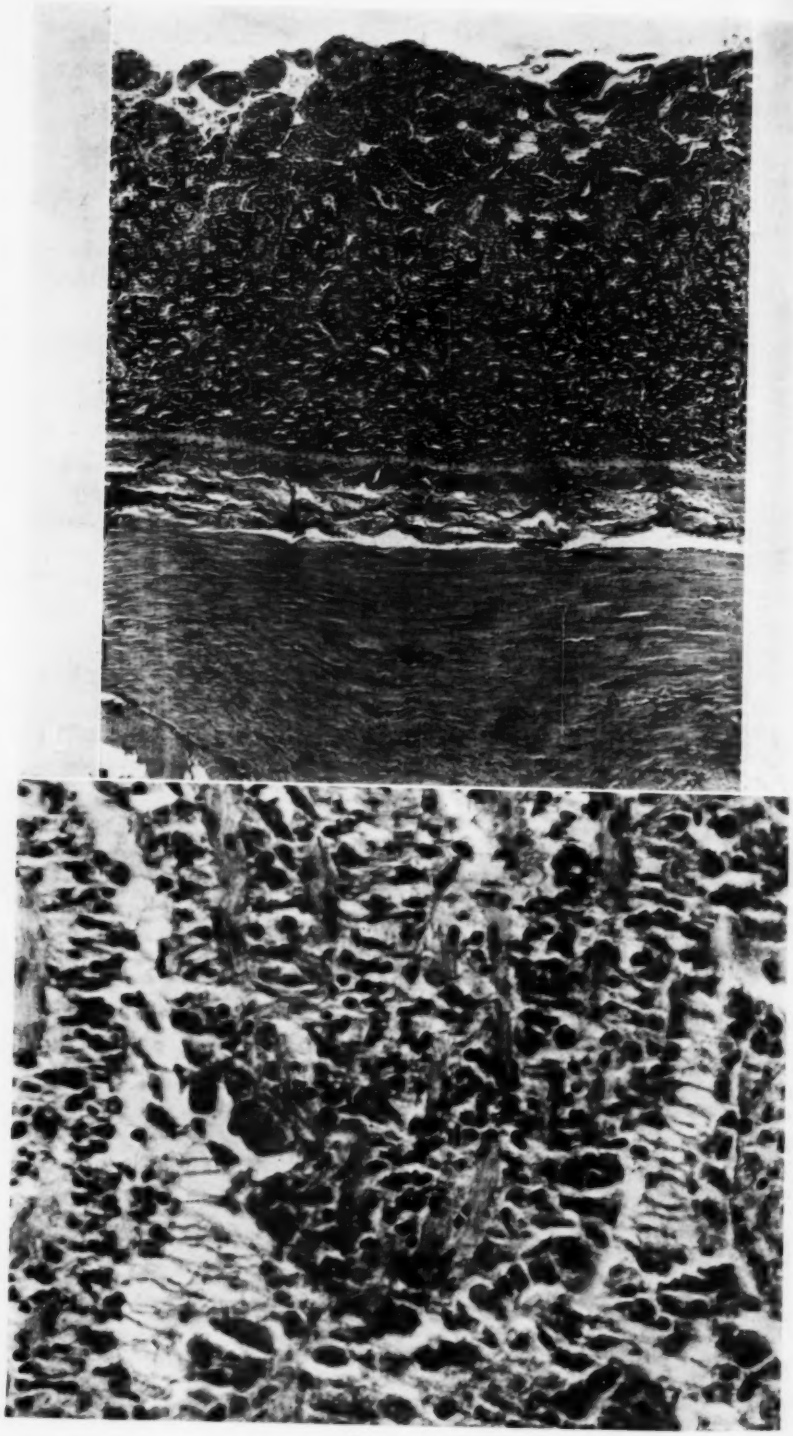
The deaths of fifteen dogs in our control series within a period of six and a half days support the numerous observations of other investigators (10, 28), etc. In nine of these dogs, there was perforation of the distended closed loop. The mucosa was, in all cases, ulcerated and infected on the antimesenteric border. The remaining six dogs had no gross perforation of the distended loop. Here again, however, the mucosa of the antimesenteric border was infected and ulcerated. The striking difference in the survival time of fifteen dogs into whose isolated obstructed jejunal loops fifty thousand units of penicillin was placed and of five additional dogs given penicillin prophylactically by intramuscular injections (Fig. 2) is unmistakable evidence for the protective action exerted by this antibacterial substance. Such animals may survive for many months after all detectable traces of penicillin have disappeared.

Several years ago, at the suggestion of Dr. Warfield Firor, Dr. Edgar Poth carried out some experiments on dogs with isolated loops in which he used sulfasuccidine. We understand that these dogs lived for long periods of time (12). The results of this work have not been published (25). Sulfasuccidine was not used in the present series of experiments because it was thought that it would be open to criticism, as it coats the mucosa with a thick insoluble paste which might interfere with normal absorption. In our experience we have found this to be true, i.e., the loops treated with sulfasuccidine become much larger over a period of weeks than the loops treated with penicillin.

The isolated obstructed loop which has been so often used in the study of the mechanism of death in intestinal obstruction and which was employed in the present experiments, is dissimilar to intestinal obstruction seen on a surgical ward in that the highly important factors of electrolyte and water loss and the presence of strong enzymes are insignificant in the former. However, in the discussion of this paper, which was presented before the Surgical Staff of the Johns

FIG. 13. Photomicrograph of section through antimesenteric border of loop of control dog 21, showing ulceration, necrosis, hemorrhage and acute inflammatory reaction. Hematoxylin and eosin, ×55.

FIG. 14. Bacterial stain of above section (Fig. 13), ×600 showing the presence of bacteria and polymorphonuclear leucocytes.



FIGS. 15–16

Hopkins Hospital, Dr. Harvey Stone pointed out that isolated loops are similar to intestinal obstruction in many respects. Often in the later stages of unrelieved intestinal obstruction the distended loops become kinked on one another, so that, in effect, one or more isolated loops may be created. Cases of volvulus and incarcerated hernial loops in which the blood supply is still intact, simulate isolated loops closely. It should also be noted that in the terminal stages of unrelieved simple obstruction the segment of bowel above the obstruction is distended, discolored, filled with bacteria and their products, and becomes ulcerated, just as in the case of an isolated loop. It is well known that cases of unrelieved obstruction that come to autopsy, usually show hemorrhage, ulceration, necrosis of the wall and often perforation of the obstructed bowel segment.

It should be emphasized that in the present experiments penicillin was used prophylactically. Whether this bacteriostatic agent would have any appreciable protective effect once infection of the intestinal wall has occurred, remains for further study.

SUMMARY

1. 100% of fifteen dogs with isolated obstructed high intestinal loops died within six and a half days. 87% died in three and a half days or less.

2. 100% of fifteen dogs in whose isolated obstructed loops penicillin was placed were protected for nine days, 93% for thirteen days and 60% for over a month, at which time these dogs were used for further experiments.

3. 100% of five dogs treated parenterally with penicillin were protected for over eighteen days. One dog lived over thirty days and indeed is well some sixty days post operative.

4. Marked distension of the loop occurring in the presence of bacteriostatic agents is compatible with life.

5. In the absence of distension of the loop, an abundant bacterial flora uninhibited by bacteriostatic agents is compatible with life.

6. These experiments indicate that distension must be present be-

FIG. 15. Photomicrograph of section through antimesenteric border of loop of penicillin treated dog 39 (loop removed four days post-operatively), showing relatively normal bowel wall. Hematoxylin and eosin, ×60.

FIG. 16. Bacterial stain of above section (Fig. 15), X600 showing absence of infection.

fore infection of the intestinal wall by the normal intestinal flora can occur.

7. Microscopic and bacteriological evidence is presented to show that penicillin given prophylactically in large doses whether in the loop or parenterally can prevent infection of the distended intestinal wall by the normal intestinal bacterial flora.

CONCLUSIONS

1. Bacteria or their products in the presence of distension are responsible for the "toxemia" and death in dogs with isolated obstructed intestinal loops.

2. Large doses of penicillin given prophylactically, whether locally or parenterally, will prevent "toxemia" and death in dogs with isolated obstructed intestinal loops, for a significant period of time.

3. It is emphasized that no conclusions regarding the efficacy of penicillin in intestinal obstruction in man can be drawn until studies on simple obstruction now in progress, have been completed.

We are deeply indebted to Dr. Arnold R. Rich for helpful criticism throughout the course of this work. We wish to express our gratitude to Dr. Alfred Blalock and Dr. Henry N. Harkins for their encouragement and help.

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PULMONARY EMBOLISM FROM OBSCURE SOURCES

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Pulmonary embolism as a complication of surgical operation and as an incident, sometimes serious, of heart disease is now well known and is not to be treated in this communication. Surgeons now recognize such an occurrence as one of their major problems, while the physician is rarely without patients with this complication of heart disease in his practice or wards.

Not much thought has been directed, however, toward the possibility that pulmonary embolism, with or without infarction of the lung, may occur as an acute condition in an apparently healthy, ambulatory individual. That such episodes might occur was postulated in 1940 by Hampton and Castleman (13), who further pointed out that the venous sources of emboli in such cases may be obscure. These authors found infarcts in the lungs in 9 per cent of 3500 patients coming to necropsy at the Massachusetts General Hospital. In another group, studied more carefully, the incidence was 14 per cent. They estimated that 30 per cent of pulmonary emboli and infarcts were derived from non-cardiac medical conditions; in this group, infarction of the lung complicated embolism of the pulmonary artery in 62 per cent of cases.

The remarkable frequency with which venous thromboses are found post-mortem has been attested by a number of writers. In one such report (Hunter et al.) (15), more than 300 careful dissections were made post-mortem for evidence of ante mortem thrombosis. One or more such clots were found in 52 per cent of the group, and 20 per cent of these showed pulmonary infarcts. Phlebothrombosis, or simple intravascular clotting, accounted for 90 per cent, while phlebitis apparently had been present in only 10 per cent of the whole. In this

* Presented at the meeting of the Association of American Physicians at Atlantic City May 9, 1944, from the Medical Service and Roentgenologic Section of the Surgical Service, Walter Reed General Hospital. Subsequent to the selection of these cases a number of similar instances of pulmonary embolism from obscure sources have been encountered.

series, however, examinations were made upon hospital patients, and the authors found that tendency to thrombosis varied directly with the length of time the patient had been at bed rest.

Since most hospital necropsies are performed on patients who have been subject to more or less bed rest, it is difficult to arrive at figures bearing on the frequency of thromboses in ambulatory persons. While the cases about to be reported were being observed at this hospital, Homans (14) published a report of similar cases collected by himself, in which he emphasized the obscurity of venous thromboses that may cause acute chest conditions, through embolism, in apparently healthy persons—attacks that simulate closely certain other cardiac and pulmonary conditions. His cases and his report, however, differ somewhat from ours, inasmuch as signs of phlebothrombosis, notably pain on dorsiflexion of the foot, were found in his cases. In ours, careful examination failed to show any sign of vascular disorder prior to the first embolic episode (with one possible exception—Case 8) and, in three, the source never became patently clear. Moreover, Homans (14) abandoned phlebography after an apparently deleterious effect in one case; we have had no serious results from this procedure, and found it very helpful in the diagnosis of several of the cases reported here. This diagnostic aid was especially important, since none of our ten patients was aware that he had ever had venous thrombosis.

Because there is often a paucity of signs and symptoms indicative of the source of the embolus, it is frequently necessary to employ x-ray visualization of the veins to detect the presence of thrombosis. The injection of Diodrast, a substance opaque to x-ray, renders the veins visible on the x-ray film. This technique is referred to as phlebography. Satisfactory phlebograms can be made at the bedside as well as in the x-ray room. This has been of importance in our experience since it eliminates the danger entailed in moving a critically ill patient. The procedure is simple. It requires no special equipment and can be completed in less than 15 minutes. The technique employed by the authors was essentially that described by Bauer (2–3) as modified by Welch, Faxon and McGahey (20).

In our experience no serious ill effects have followed the procedure. Vomiting and urticaria occurred in a few instances. In 164 visualizations we have observed no serious hypersensitivity to Diodrast. Mild

local phlebitis, due to Diodrast, occurred at the site of injection on three occasions. Up to the present we have observed no aggravation of pre-existing thrombophlebitis, and no embolism following phelbography.

Phlebograms of the lower extremities show all the major venous pathways from the ankle to the pelvis. This includes the anterior and posterior tibial, the popliteal, femoral and frequently the iliac veins. Phlebography shows whether the vein is patent or not, whether the lumen is normal or recanalized, whether collateral venous circulation exists and, if so, its extent. Absence of filling of a vein or segment of a vein indicates the presence of thrombosis. The validity of the interpretation rests upon a wealth of objective evidence. Operative removal of thrombi from veins showing such filling defects has been reported by Welch (20) and his co-workers, DeBakey (7), Fine (11), Bauer (2–3) and Griswold (23). Unfortunately, incipient thrombosis in the plantar and calf muscle veins cannot be detected by phlebography, since it is only after the thrombus has involved one of the major venous channels that its presence is revealed.

Error in interpretation may arise from an apparent filling defect in the popliteal vein due to hyperextension of the knee during the injection. A convex filling defect frequently seen in the upper third of the thigh is produced by the pressure of the femoral artery on the femoral vein. Venous spasm resulting from apprehension, irritation of the contrast substance, or vein puncture may give rise to narrowing, or, in extreme cases, to obliteration of the deep veins, according to some authors (21).

In spite of the suggestion of Hampton and Castleman (13) that acute pulmonary embolism probably affects certain apparently healthy persons, we were forced to admit, when our patients were being observed and diagnosed, that we had had little or no experience of acute episodes of this nature in civilian practice. In retrospect, it seems likely that many had been overlooked.

The roentgen diagnosis of pulmonary infarction is dependent upon an accurate knowledge of the gross pathological findings. The following principles should guide the roentgenologist in their recognition.

Infarcts are ill defined or not seen at all during the first four to twenty-four hours. Repeated daily examinations are therefore neces-

sary. The lesion is always in contact with a pleural surface either at the interlobar fissures or at the periphery of the lung. Two or three pleural surfaces are commonly involved by a single infarct; for example, at the junction of fissures or at the costophrenic angles. The long diameter of an infarct is always parallel to the largest pleural surface involved. The medial or cardiac margin of an infarct is convex or "hump" shaped and sharp in outline when projected on edge. Oblique and lateral views of the chest are often necessary to obtain profile views and thus demonstrate the lesions. Pleural effusion may or may not be present and if present obscures the lesion for a few days. Incomplete infarcts may disappear within two or three days, whereas complete infarction usually persists for two to three weeks and heals by linear scarring. Large infarcts may persist for months with very little change.

Case 1. A fifty year old, white officer was admitted November 4, 1942, with fever and pain in the right axilla; admission diagnosis was "primary, atypical pneumonia." Being an officer of the Regular Army, the patient had doubtless been examined on numerous previous occasions. The past history was irrelevant. He rarely drank. There was no known phlebitis and there were no significant varicose veins. Symptoms began during foreign duty in June 1942 and were protean, consisting of diarrhea, vomiting (on one occasion hematemesis), a dry cough and fatigability. During the summer he was treated with massage for "prostatitis." He had intermittent cough, chilliness and seemed feverish at times. En route to this country he developed the symptoms complained of on admission, as well as giddiness and shortness of breath. There was no cough. Examination showed a vigorous man, who was in good general condition except for an area of consolidation at the base of the left lung. Roentgenogram confirmed the diagnosis by showing two areas of infarction at the left lung base, with a small adjacent effiusion. There was a mild anemia, incurred from previous hematemesis. Leucocytes numbered 17,000. The electrocardiogram was normal. Erythrocyte sedimentation rate was 22 millimeters per hour on November 11, rising to 28 millimeters on November 20. Maximum temperature was 101.6° F. (on the fourth day). The signs resolved and the patient recovered. On November 20, the symptoms recurred, with the addition of a small amount of blood streaked sputum and signs of fluid over the consolidation. A diagnosis was then made of repeated infarction of the left lung base. The temperature again subsided in seven or eight days, and the patient seemed well. Suddenly on the night of November 30 he suffered acute dyspnea and, in spite of oxygen therapy, died in less than two hours. Necropsy (Lt. William S. Randall). Diagnoses: 1. Thrombosis, multiple, of prostatic veins, cause undetermined. 2. Thrombosis, pulmonary artery, severe, secondary to No. 1, duration 1½ hours. 3. Infarction, multiple, left lung, secondary to No. 1.

Multiple infarcts were found in the left lung, and there was moderately severe, bilateral pulmonary edema and congestion, and a moderate degree of patchy atelectasis, secondary to infarction. The prostate was slightly hyperplastic, the kidneys moderately congested. 300 cc. of thin, sanguineous fluid was found in the left pleural cavity. Liver, spleen and kidneys were grossly normal. The heart was of normal appearance, with some dilatation of the left ventricle (considered by the pathologist to be of no practical significance). There was no coronary artery disease. A few small emboli were found in branches of the right pulmonary artery. Microscopic examination added nothing of importance.

The pulmonary artery contained a large growing thrombus extending into the right and left branches, straddling the bifurcation, and the two fragments measured 10 and 11 centimeters respectively. A portion of this was yellowish-gray, while the larger part was dark purple. The pulmonary artery thrombus was apparently a propagating clot that grew *in situ* on the basis of an embolus. As there was no evidence of other venous thromboses, those in the prostatic and periprostatic veins, which were extensively involved, were considered the likely source of emboli, since these veins drain through the middle hemorrhoidal veins into the internal iliacs. Without phlebograms, however, the leg veins cannot be entirely disregarded as a possible seat of thrombosis.

Case 2. A 56 year old officer, white, was admitted by transfer October 9, 1942, without current symptoms but with a history of having had a recent massive pericardial effusion. This patient smoked two packages of cigarettes daily, took an occasional drink. His family history was good. The past history was uneventful; the right little toe had been amputated in 1910 for deformity. During June and July, 1942, the patient felt below par but had no specific symptoms beyond fatigability. On August 10, he felt chilly and developed pain in the left shoulder behind, aggravated by breathing and movement. The temperature rose to 102° F. during the afternoon. By evening, pain had shifted to a point just medial to the left nipple. On admission to the post hospital, breath sounds were suppressed over the left upper chest anteriorly, where a few fine rales were heard. A questionable friction rub was noted in the left interscapular area. Pneumonia was suspected. Laboratory studies were normal save for a leucocytosis of 11,000. Blood pressure was 170/108. Roentgenogram of the chest showed lungs clear and heart and great vessels normal in size and configuration. Low grade fever persisted. Because of pain about the cardiac apex an electrocardiogram was made; this showed only slight elevation of the S-T intervals in Leads II and III, and some limitation of amplitude of the main ventricular deflections, which reached a maximum of 7 millimeters in Lead II. Numerous tracings were made, both at the post hospital and at Walter Reed; the early S-T changes disappeared promptly and the tracings continued normal, though the Q-R-S complexes continued to extend about 4–7 millimeters in the limb leads. At times, the T waves were somewhat reduced in Leads I and IV. On August 28, a roentgenogram showed marked enlargement of the cardiac shadow, leading to the diagnosis of pericardial effusion. By September 7, however, the heart, by roentgenogram, had returned practically to its original size.

The patient recovered and was transferred to this hospital for disposition. Physical examination showed nothing abnormal save a moderate emphysema. The heart was not enlarged on percussion, and the sounds were normal. Roent-

FIG. 1

FIGS. 1 AND 1A. Normal phlebogram (fig. 1) and descriptive sketch (fig. 1A) showing the deep venous trunks of the leg and distal third of thigh.

genogram showed heart and lungs normal. The patient was ambulatory, when, on October 19, he complained of pain and tenderness in the left popliteal space and a diagnosis of popliteal vein thrombosis was made. Treatment consisted of elevation and application of moderate heat. In three days the leg was much im-

proved. During this phase of thrombosis the sedimentation rate of the erythrocytes was 22 millimeters per hour, compared with one of 4 millimeters on admission. On October 25 the patient developed the same series of symptoms as were noted at the onset of the first attack. A friction rub was heard just inside the left mid-

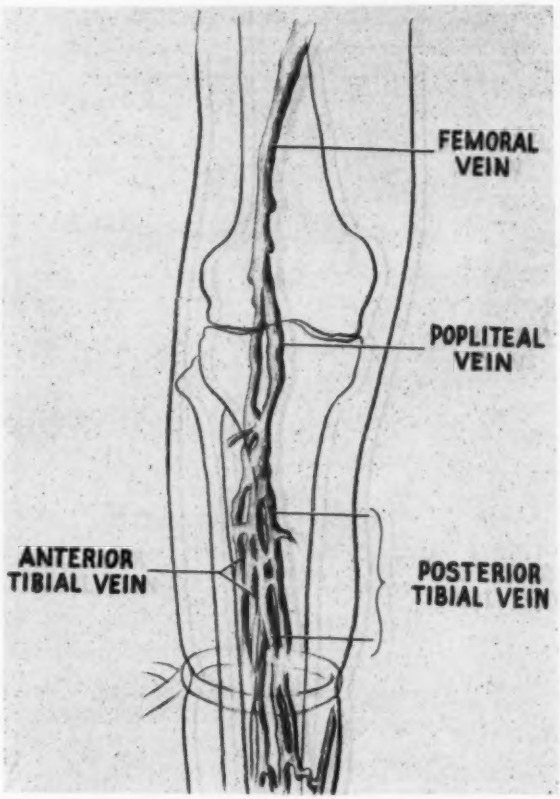

FIG. 1A

clavicular line at the heart's border. Roentgenogram of the chest was normal at this time. On the following day the patient developed a purulent pansinusitis. Low grade fever persisted. A diagnosis of pulmonary embolism, without infarction, or with incomplete or undetectable infarction was made, because of the recent thrombophlebitis. On November 18, roentgenogram showed that the heart had

increased 2 centimeters in diameter. By November 26, the heart shadow had again returned to normal. On December 1, 1942, the officer developed acute conjunctivitis of the right eye, and, on December 5, an acute iritis in the same eye. Phlebograms were made December 11 and showed normal venous pathways in the

FIG. 2

FIGS. 2 AND 2A. Normal phlebogram (fig. 2) and descriptive sketch (fig. 2A) showing femoral and external iliac vein.

right leg; on the left there was definite narrowing of the channel of the popliteal vein at the site indicated by the symptoms.

It is believed that this officer suffered two attacks (one before and one during treatment at this hospital) of pulmonary embolism from the left popliteal vein, in the course of which the lung was only partially infarcted while the heart was acutely dilated. The patient recovered and returned to duty.

Case 3. A 44 year old white officer, entered the hospital 4 August 1943, complaining of severe precordial pain, radiating to the left shoulder and aggravated by breathing. The family history was excellent. The patient smoked a pack of cigarettes daily but drank practically no alcohol. He had suffered a "nervous

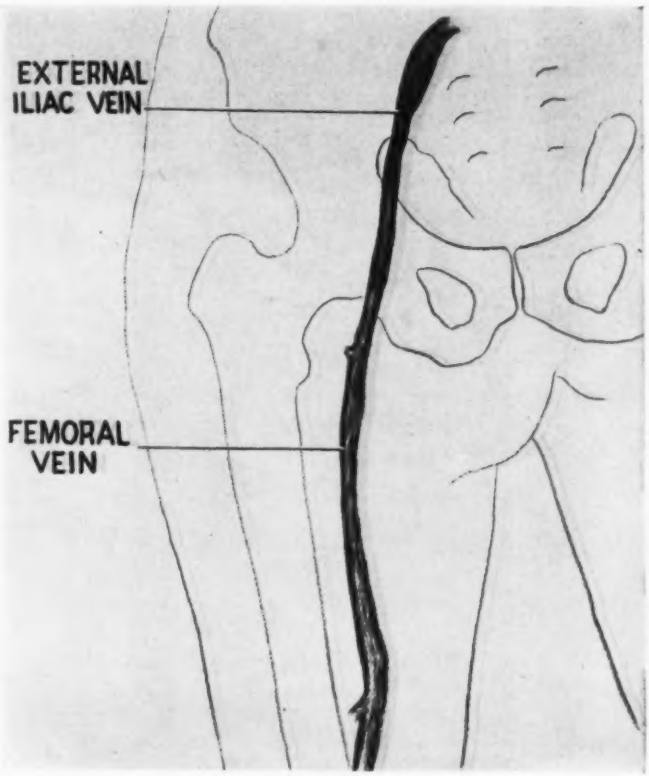

FIG. 2A

breakdown" in the past, had had an appendectomy in 1923; after this operation he had frequent indigestion, but no organic disorder was found except hemorrhoids. On the morning of his present admission he had sudden onset of the pain noted above. Ruptured peptic ulcer was suspected by an outside physician, who recommended the patient be admitted to hospital. The blood pressure was 160/100 before admission, 138/82 shortly after entry. A few hours after entering

the hospital the patient coughed up a small amount of blood streaked sputum. Percussion note was impaired at the left base, breath sounds were distant, and a few crepitant rales were heard. The heart was normal on physical and electro-

FIG. 3

FIGS. 3 AND 3A. Phlebogram (fig. 3) and explanatory sketch (fig. 3A) showing occlusion of deep venous trunks in left calf in Case 2.

cardiographic examinations, the tracings being identical with records made in 1942. The liver was felt one fingerbreadth below the rib margin. Physical examination was otherwise normal. There was no clinical evidence of phlebitis. By the third morning some fluid had appeared at the base of the left lung and there were moist rales at the right base. On the day after admission the tempeature reached 99.2°

F. and it rose to 100.0° on the eighteenth day. Otherwise it was consistently normal. Bilateral pulmonary infarction was suspected, though Homans's sign remained negative and no indurated or tender veins were found. Diagnosis of

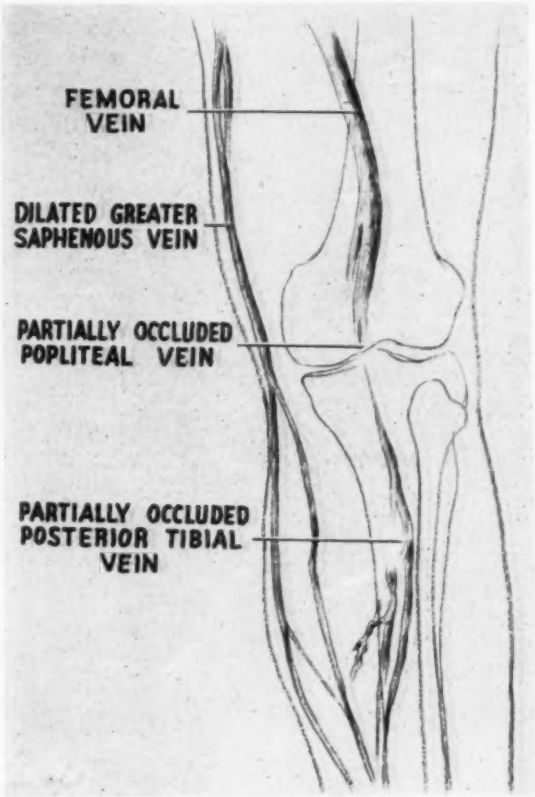

FIG. 3A

bilateral pulmonary infarction was concurred in by the Department of Roentgenology. On the day after admission, the leucocyte count was 9,800; this rose to 10,500 on the third day. The sedimentation rate was 42 millimeters six days after admission. Urinalyses, serologic tests and blood counts otherwise were normal. Dicumarol therapy was instituted one week after admission, 300 milligrams being administered on each of three consecutive days. Prothrombin con-

centration fell to 22 per cent of normal after administration of the second dose. Subsequent levels varied between 22 per cent–54 per cent—the prothrombin concentration returning to normal ten days after institution of anticoagulant therapy.

FIG. 4

FIGS. 4 AND 4A. Phlebogram (fig. 4) and explanatory sketch (fig. 4A) showing tortuous collateral veins, by-passing occluded femoral vein in Case 3. Note patent iliac vein.

This patient was thought to have had at least two pulmonary infarctions. The origin of the emboli was obscure until phlebograms showed an old femoral vein occlusion on the left, compensated for by an elaborate collateral circulation. This patient recovered and returned to duty. At no time was any acute or active thrombophlebitis found, except by inference.

Case 4. A 34 year old, white officer, entered the hospital 2 September 1943 from overseas, with a transfer diagnosis of metastatic carcinoma of the lungs. The patient's father died at 52 of coronary occlusion; the mother was living, subject to asthma. The past history revealed that the patient had had good general

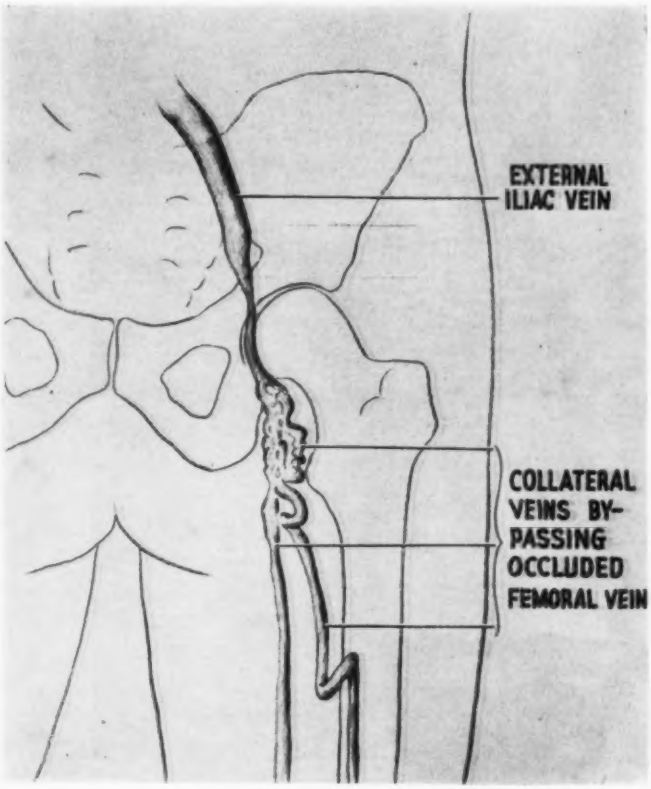

FIG. 4A

health. On two occasions he had sought treatment for thrombosed hemorrhoidal veins. Tonsillectomy and adenoidectomy had been done at the age of 8. On August 13 this officer had run about five miles for exercise. Being a roentgenologist, and having just established his apparatus overseas, he had a film of his own chest made August 14 in order to test the machine. He was shocked to find that the film showed rounded shadows very suggestive of metastatic tumor.

This diagnosis was concurred in at an overseas hospital and also at the Walter Reed General Hospital, though a roentgenologist in each place suggested the possibility of multiple infarcts of the lungs. In retrospect the patient thought he

FIG. 5

FIGS. 5 AND 5A. Phlebogram (fig. 5) and descriptive sketch (fig. 5A) showing occlusion of anterior and posterior tibial veins in Case 7. The femoral vein is partially occluded in its distal third.

had not felt entirely well for three weeks before setting up his apparatus, being rather readily fatigued. The patient thinks he had fever as high as 100° F. for a few days during the week following the making of the first chest film. He lost weight from anorexia. There was no sputum and no chest pain. About six weeks

after onset of his troubles he had a recurrence of thrombosing hemorrhoids. He had a hacking, unproductive cough. For two weeks before arriving at Walter Reed General Hospital he had had a dull, intermittent pain in the left loser axilla and in the right nipple region. On admission, physical examination was negative.

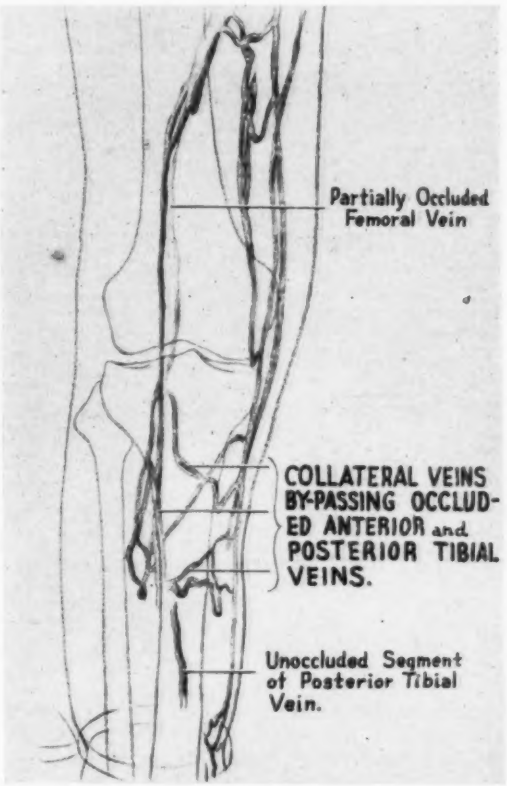
Partially Occluded Femoral Vein
COLLATERAL VEINS BY-PASSING OCCLUDED ANTERIOR and POSTERIOR TIBIAL VEINS.
Unoccluded Segment of Posterior Tibial Vein.

FIG. 5A

Blood pressure was 120/80, pulse 80, regular. The maximum mouth temperature was 99° F. (in September). Intravenous urograms, urine, roentgenograms of the entire skeleton, serologic tests and stool examinations were normal. Blood counts were normal. On the third day at Walter Reed General Hospital the sedimentation rate of the erythrocytes was 38 millimeters per minute, rising to 41 a few days later. Reaction to a skin test with tuberculin (P.P.D. 0.00002 mgm.) was

"double plus" in 48 and 72 hours. Six weeks after admission the sedimentation rate was 4 millimeters. Gradual recession of the pulmonary shadows in the patient's chest, together with other evidence brought out by plain and contrast roentgenograms indicate that he was probably suffering from multiple infarcts of the lungs. After a sick leave and reassurance the officer returned to duty at a hospital where he could be under observation. Phlebograms of the legs were normal. This patient was re-examined by us in May 1944: he was entirely well,

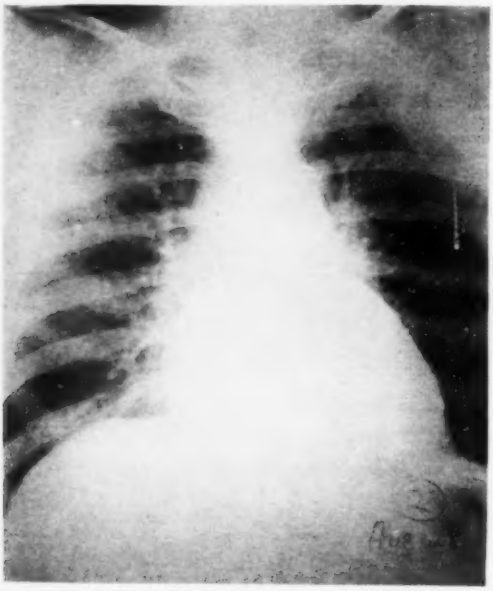

FIG. 6. CASE 2. TRANSFER TELEROENTGENOGRAM OF HEART, BELIEVED TO BE DILATATION INCIDENT TO PULMONARY EMBOLISM

except for occasional sticking pain at the level of the left diaphragm. The only clue to the source of pulmonary emboli was in the occurrence of thrombosing hemorrhoids shortly after the onset of the illness. A similar occurrence will be found noted at the onset of symptoms in Case 8.

Case 5. A 61 year old officer entered this hospital October 1, 1942 and was ill intermittently until March, 1943.

Details of this officer's history are not available but his general health had been good and he had no knowledge of previous phlebitis. At onset, the patient had pain in both shoulders. Later, he was conscious of dyspnea. Physical examination showed nothing unusual except areas of consolidation occurring repeatedly in

each side of the chest, with practically no rales to be heard and little or no cough. Maximum leucocyte count was 16,400. The blood pressure was 102/76. Sedimentation rate of the erythrocytes was 1 millimeter at entry, rising to 24 millimeters per hour, falling finally to 3. Blood culture and chemistry showed nothing abnormal. The Wassermann reaction was negative. All other tests were negative or within normal limits. Serial electrocardiograms showed a normal picture at

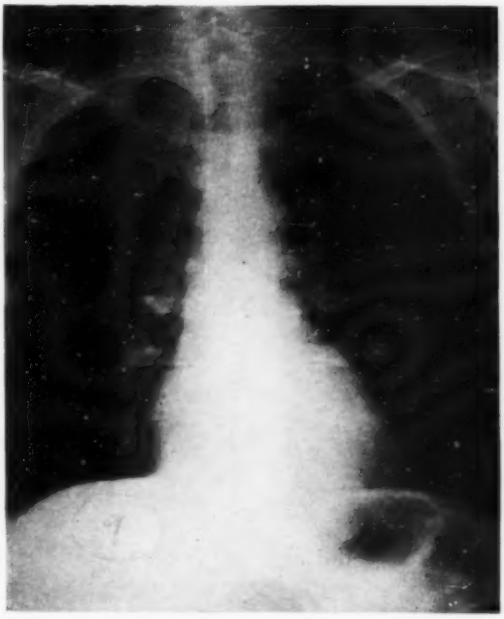

FIG. 7. CASE 2. RECURRENCE OF LESSER DEGREE OF CARDIAC DILATATION FOLLOWING PULMONARY EMBOLISM AT WALTER REED GENERAL HOSPITAL

onset, and a slight elevation of the S-T intervals in Leads I and IV on the following day. T_4 became inverted on the fifteenth day. On the twenty-third day, auricular flutter was noted. T_1 became flattened. Before discharge, the tracing had returned to normal. This officer suffered a series of repeated pulmonary infarctions with characteristic roentgenologic findings, some of huge size: one seemed to involve all or most of the right lower lung lobe. After the acute symptoms had subsided, phlebograms were done on December 3, 1942, two months after onset. They proved to be quite normal. January 9, 1943 the patient had another pul-

monary infarct while on sick leave. By February 1943 he had noted considerable swelling of both legs, and, on reporting to the hospital, was found to have a phlebothrombosis of the left lower leg. He was then placed on Dicumarol therapy, and his prothrombin concentration maintained at levels varying between 38 and 52 per cent of normal, for a period of 12 days. He had no further emobli and returned to good general health, except for bilateral swelling of the legs. In retrospect, it appears likely that the series of attacks of pulmonary infarction, extending over more than three months time, were derived from emboli thrown off from throm-

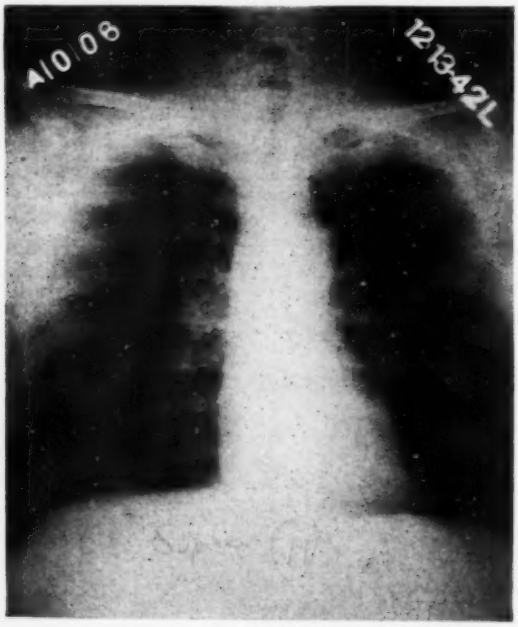

FIG. 8. CASE 2. EVENTUAL (PERMANENT) SIZE OF HEART

boses in the pelvic veins. It was not until four months had passed that the degree of thrombosis was sufficient to cause obstruction to venous flow from the legs.

Case 6. A very active 61 year old officer was admitted December 30, 1942 by ambulance, complaining of severe pain through the mid-chest, aggravated by walking. The family history was irrelevant. There had been no tropical disease, except a single attack of malaria in 1925, in spite of three tours of tropical service. The officer smoked and drank in moderation and had had good health until he suffered a bilateral "pleurisy" in 1933, followed by bilateral "pneumonia." He also had mild "pneumonia" in March 1942.

On the day of his admission, this officer ran to a waiting automobile, in which he was taken to his office. The exertion caused a severe constricting pain about the chest, which became somewhat better while he was quiet but which returned whenever he walked. Because of the crushing and smothering character of the pain and his general prostration, he reported to a medical officer. An electrocardiogram was made, which was reported as "compatible with coronary occlusion," and the patient was sent to this hospital.

The patient was slightly cyanotic but was not shocked. Blood pressure was 140/90. Pulse was regular, 80 per minute. There was dullness, tubular breathing and increased tactile fremitus at the left lung base. The heart was normal on physical examination and the examination otherwise was normal. The diagnosis was debated: did the officer have coronary occlusion with thrombus formation in the right heart and emoblism to the lung, or did the embolus reach the lung from elsewhere? A week after admission, phlebograms of the legs were made and found normal. The temperature rose to 99.4° F. on the morning after onset and reached a maximum of 101.3° F. on the following afternoon. Thereafter, it was only slightly and occasionally elevated. Electrocardiograms: on the day of admission the tracing showed iso-electric T_2 and T_3 and a marked levogram. On the next day T_1, T_2 and T_3 were all flattened. T_3 thereafter became inverted and the other T waves showed a normal upright appearance. Subsequently, T_3 became upright or iso-electric. These findings, with the positive findings of consolidation at the left lung base, were considered evidence of pulmonary infarction rather than coronary occlusion. Fluid appeared at the left base, and the patient, during his course, had pain and signs of infarction at the right lung base as well. Roentgenograms showed bilateral basilar infarctions with a rather large cardiac shadow that receded markedly in size as the pulmonary lesions regressed.

On admission, urine and blood were normal except for leucocytosis (13,600 to 22,100). The leucocyte count six days later was 6,500. Blood chemical and serologic tests were normal, though the blood urea was 16 milligrams per 100 cc. (normal 10–15). As we have made a practice of giving sulfadiazine, on rather empirical grounds, hoping to protect the patient against secondary lung infection during the first period of infarction, this drug was used and a good level in the blood attained. Sedimentation rate of the erythrocytes two weeks after onset was 12 millimeters per hour, rising to 26 millimeters two weeks later.

In spite of normal leg phlebograms and the absence of a demonstrable source of his embolic manifestations, the diagnosis of bilateral pulmonary infarction was finally made. In retrospect, it would seem that the previous attack of bilateral "pleurisy and pneumonia" and the subsequent mild "pneumonia" were, in all probability, attacks very similar to the one for which he was treated here.

This officer's blood pressure rose substantially during convalescence. He remained symptom-free after the acute phase of his illness and was returned to duty.

Subsequently this patient was observed to have developed a sudden increase in the caliber of the thoracic aorta. Roentgenologic examination led to the

diagnosis of dissecting aneurysm. The officer died at a later date and an extensive dissection of the thoracic aorta was found beginning in the transverse arch and progressing toward the heart, finally leaking into the pericardium and causing death. An older dissection beginning at a point just below the left subclavian artery was found to have extended as far as the abdominal aorta. The only apparent residuals of previous pulmonary infarction consisted of pleural adhesions at the lung bases.

Case 7. A 58 year old officer was admitted with pneumonia June 12, 1943. Family history revealed nothing pertinent. Tonsillectomy in 1922, hemorrhoidectomy in 1935 and appendectomy in 1936 were recorded. The officer had smoked four packs of cigarettes prior to 1940, none since. He took two highballs daily. He recalled diphtheria and scarlet fever and said he had had a "gouty arthritis" for ten years. He had excision of synovial membrane of the right knee in 1940 as a result of injury in 1936. In none of these episodes nor at any other time was there history of phlebitis.

Present illness began five days before admission, with chill followed by fever, to 104° F. This was followed on the second day by substernal pain and cough. Blood streaked sputum yielded type II pneumococcus. On admission, dullness, suppressed breath sounds and numerous rales after cough were found over the right upper lobe. Blood pressure was 104/48. There were gouty deformities of hands and feet. Temperature was 102°, pulse 98 per minute. The examination being otherwise essentially negative, a diagnosis of lobar pneumonia, right upper lobe, was made.

Sulfadiazine was administered, and a blood level of 11.16 milligrams per 100 cc. of blood was obtained in two days. The temperature fell but did not become normal. Two days after admission rales were heard at both bases followed by bilateral effusion, above which were heard bronchovesicular breath sounds. Three days later, patient had sharp pain at the right lung base, and a friction rub became apparent at this area. The prostate was eliminated as a possible source of emboli. On June 29, phlebograms showed absence of filling of the left femoral vein and of the anterior and posterior tibial veins. At the onset of signs in the bases of the lungs, the electrocardiogram was normal, excepting low voltage of Q-R-S complexes in limb leads (maximum 7 millimeters). Three days later, T_3 became inverted, returning to the iso-electric level two days later. On admission the leucocytes numbered 12,200 per cubic millimeter, returning shortly to normal. Throughout the duration of the pulmonary infarctions, they were never above 9,300. Urine, blood chemical and serologic tests, and blood culture were normal; there was a mild anemia on most counts. Six days after onset of the signs of infarction the erythrocyte sedimentation rate (corrected) was 34 millimeters per hour.

Serial roentgenograms showed that the consolidation in the right upper lobe cleared promptly in a manner typical of pneumonia. The basilar consolidations and effusions (bilateral) receded much more slowly. The heart appeared dilated during the course of the illness.

In this case, the diagnosis was made of lobar pneumonia (right upper lobe),

complicated by bilateral infarction of the lung bases. The previously thrombosed venous channels in the left leg were considered the likely source of emboli. The officer recovered and returned to duty.

Case 8. A 58 year old officer was admitted 23 March 1944 without complaints, and with a diagnosis of coronary sclerosis and angina pectoris. The family history was irrelevant. The patient had "active tuberculosis" from 1919 to 1926,

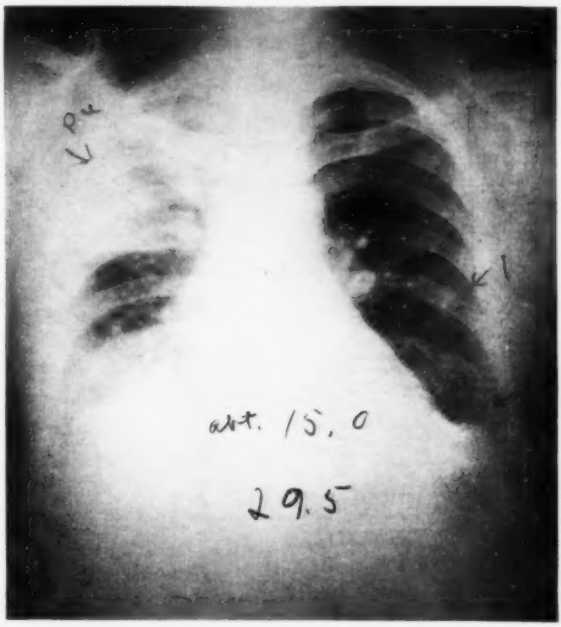

FIG. 9. Case 7. Showing lobar pneumonia at right upper lobe complicated by infarcts in both lung bases. Rather large cardiac shadow is common in pulmonary embolism.

when it became "arrested." He continued at work during this time. There was no other serious illness except pneumonia in 1919.

This officer entered active duty in 1941 in excellent health. He went overseas in May 1943 and engaged in active duty in a staff position. In August he entered a hospital and was treated for malaria; he was at partial bed rest for thirteen days. After discharge, he failed to recover his physical and mental enthusiasm. He was easily fatigued, had poor appetite, and noted dyspnea on exertion. There were some chest pains, but he did not associate them directly with exertion. On

January 8, 1944 he crossed a mountain in a car and was quite "uncomfortable" through the chest; he was dyspneic and had slight precordial pain. He entered a hospital, where he developed a sharp, stabbing pain in the region of the cardiac apex and left axilla; this was markedly exaggerated on breathing. Coincident with the onset of his other symptoms, the patient was found to have a thrombosed hemorrhoid. He had never suffered from hemorrhoids previously. The thrombosed pile was removed under local anesthesia at the time of admission to hospital. A few cysts suggesting Endamoeba histolytica were found after an attack of bloody diarrhea; however, he received no specific therapy and repeated subsequent examinations showed normal stools. General physical examination was not recorded, but examination of the heart showed nothing abnormal. Roentgenogram of the chest showed a somewhat enlarged heart. Blood pressure was 162/105. The temperature, pulse, respiration, urine and smears for malaria were all negative. Leucocytes numbered 12,200, with 75 per cent polymorphonuclear cells. Sedimentation rate of the erythrocytes was 13 to 15 millimeters per hour. An electrocardiogram 29 January 1944 showed absence of visible T waves in all limb leads, with upright normal waves in Lead IV. Otherwise the tracing was normal. A previous tracing (January 10, 1944) had shown a slightly upright T_1; otherwise the records on January 10 and 29 were identical. The diagnosis of coronary sclerosis and angina of effort was concurred in by other examiners prior to entry into this hospital.

Here, physical examination showed a large, vigorous man, thirty pounds under his usual weight of 210 pounds. He was asymptomatic. He had had no pain or any other symptoms referable to the legs or the venous system. The throat was injected, and there was some postnasal catarrh. Blood pressure was 165/90. Examination otherwise was negative. The legs showed no varicosities, no tenderness or swelling. Homans's sign was negative. Electrocardiogram showed upright T waves in Leads I, II and IV, those in IV being of greater amplitude than formerly. T_3 was slightly inverted. There was predominance of the levogram with a small Q_3. The tracing was well within normal limits. Roentgeogram of the chest showed scars in the left lower lung indicative of previous infarction. Before roentgenography, the clinical impression had been that the patient probably had had previous pulmonary infarction. In favor of this were the cardiac enlargement, the nature of his pain and the electrocardiograms. Phlebograms were made of the legs and found normal. As in Case 4, the only clue to the source of emboli was the occurrence of a thrombosing hemorrhoid, in the present case at the very onset of chest symptoms.

This officer being considered as well, he was returned to duty.

Case 9. A 45 year old wife of an Army Captain, was admitted to hospital 21 March 1944, with complaints of pain in the left side of the chest and expectoration of blood. She did not appear seriously ill.

There was nothing of note in the family history. The patient had had no children. She had an appendectomy in 1932 and a "kidney infection" in 1943. She reported four attacks of pneumonia—in 1932, 1938, 1939 and January 1944.

In each case, the "pneumonia" was followed by "pleurisy." Breast tumors, apparently benign, were removed in 1940, 1941 and 1942. After one of these minor operations she was told she had a "false pleurisy" due to blood clot. There was no history of phlebitis.

On admission, March 21, 1944, physical examination revealed dullness without rales at the left lung base behind. Otherwise the examination was negative.

Blood pressure was 130/78. Four days later it was noted that she was expectorating about an ouce of thick yellow sputum each morning. The red blood cell sedimentation rate was 38 millimeters one week after admission. Blood count on admission showed only 5,300 leucocytes per cubic milimeter, with 80 per cent of polymorphonuclear cells. Sputa were negative for tubercle bacilli.

This patient had had her fourth attack of "pneumonia" in this hospital in December 1943 and January 1944. The diagnosis of pneumonia was made on that occasion in spite of the lack of bacterial confirmation, as the patient had a large area of consolidation at the right lung base, temperature up to 102.8°F.; she recovered under sulfadiazine. However, the history of repeated attacks, all associated with prolonged pleural pain, suggested repeated pulmonary infarction, and this diagnosis was made on the March admission. Films of the patient's admission of three months before were reviewed and a picture very suggestive of infarction was found.

Careful examination of the extremities failed to show any unusual finding in the venous system. Nevertheless, phlebograms of the legs were made in a search for a possible source of emobli. These were normal. In this case, the source of emboli remains obscure.

Case 10. A 48 year old member of the W.A.C. entered the hospital April 21, 1944 for a "cold" of three days duration. There was slight sore throat and hoarseness. The past history revealed nothing of importance except as noted blow. The patient had never had trouble with her legs in any manner, to her knowledge. The legs had never swollen and she had always been quite active. There were no varicosities.

Examination at the bedside was quite normal, excepting some local upper respiratory congestion. Her temperature was not above 99.2° F. Blood counts, serologic test and urinalysis were normal. The electrocardiogram was normal throughout the limb leads; in Lead 4-F the T wave was diphasic.

This patient had been in a hospital about January 1, 1944, with a cold and a bruise of the right hip following a fall. Shortly after discharge on January 12, 1944, she had a pain to the left of the sternum; at this time she raised a small amount of blood streaked sputum on two or three occasions. However, she continued at work and did not enter a hospital again until April 21, when she became sick on furlough and entered Walter Reed Hospital.

During this admission, though there were no acute symptoms except the upper respiratory infection, a routine chest roentgenogram was made. Evidence of previous infarction of the lung was found and, as there had been no chest symptoms since January, it was assumed that the shadow at the left lung base was an infarc-

tion of three months standing. The heart showed a transitory dilatation and this with the electrocardiographic change (T_4) suggest the possibility of a more recent asymptomatic infarction. Phlebograms showed thrombosis of the medial branch of a double femoral vein of the left leg.

Analysis shows, that eight of these patients are white males, two white females. They fell, by age, as follows: 1 in the fourth decade, 3 in the fifth, 4 in the sixth, 2 in the seventh. Five were officers of the Regular Army, three officers of the Army of the United States, and two were women. No specific common denominator that could reasonably be supposed to have caused phlebothrombosis and embolism was elicited. It seems likely, however, that Regular Army officers, as a class, indulge in more strenuous exercise than almost any other class of men of comparable age; one A.U.S. officer had run five miles on the day before pulmonary emboli were detected, while another A.U.S. officer developed pulmonary infarctions during pneumonia and is, therefore, the only patient in this series whose embolism was not known to be the initial incident. The remaining officer was fatigued and had developed hemorrhoids for the first time. One, naturally, wonders whether vigorous exertion, to which Regular Army officers are singularly devoted, played a rôle in the events described in five of the above cases—so called "effort thrombosis." It would be of interest to know whether pulmonary embolism from silent sources is facilitated by vigorous exercise in middle aged men, and whether this explains the occurrence of this syndrome in our cases, when similar cases in civilian life have not been encountered sufficiently often to lead to their recognition. In the case of one A.U.S. officer, the long run might be suspected of having dislodged an embolus. In all these cases, however, the question of the rôle of exertion must be left open.

Heavy drinking has, in the past, seemed to one of us to predispose to phlebothrombosis in some individuals, but, in our patients, none gave a history of more than occasional to moderate drinking.

The salient features of these cases that prompted this report are: first, the male patients were all stricken while on duty and in vigorous or, at least, reasonably good state of health; second, none was aware of having had any disorder of the veins, either previously or at admission to the hospital; third, at the time of admission there was no obvious sign of venous thrombosis (excepting Case 8) in any case.

Accurate diagnosis in such cases is exceedingly difficult at onset. None of our patients was admitted with a correct diagnosis. One was thought to have primary, atypical pneumonia, one pericarditis with effusion, one ruptured peptic ulcer, one carcinoma of the lungs (metastatic), two coronary occlusion, one angina pectoris; in one case, the infarctions occurred with, or shortly following, the onset of lobar pneumonia, which was correctly diagnosed, while in one the admission diagnosis of pneumonia was not substantiated. Roentgenograms of the chest are not very helpful at onset, since the shadow of infarction does not develop until a day or two have elapsed; however, the finding of an enlarged cardiac shadow is in favor of pulmonary embolism, unless there is some other explanation of its presence. In general, dyspnea is more prominent than pain, but in many cases we have found it impossible to differentiate pulmonary embolism from coronary occlusion at onset on the basis of symptoms alone. A dull pain in the base of the neck or in a shoulder, followed by pain in an axilla, should always suggest pulmonary embolism. Elevation of temperature within twenty-four hours of the first symptom is rather more suggestive of embolism than of coronary occlusion. Blood-splitting may prove very helpful, but this occurs in less than half the cases of embolism, and, then, only after infarction has occurred, hence is not helpful at the onset. The most difficult differentiation in our experience is between embolism from a silent peripheral source and embolism from myocardial infarction.

A pleural friction may develop without complete infarction and without clear roentgen findings. A friction rub along the heart's border or even over the heart itself may lead to the erroneous diagnosis of pericarditis and give weight to the possibility of coronary occlusion. We have recently seen a patient with repeated, frank postoperative pulmonary infarction, in whom the friction rub was confined to the precordial area. In this case, however, the rub was coarse and lasted two or three days, in contradistinction to the dry, evanescent rub usually found in myocardial infarction—when found at all.

Serial electrocardiograms and phlebograms, in expert hands, usually elucidate the diagnosis. In our cases, electrocardiographic changes included—flattening of T waves in Leads II and III or in all leads, inversion of T_3, early elevation of the S-T intervals in Leads II and

III; the T waves may be flattened in all limb leads and remain normal or somewhat reduced in Lead IV. In two of our cases the tracings were normal. In one, the T waves were sufficiently inverted to suggest myocardial infarction. However, the typical series of events found in the course of coronary occlusion is never found, at least in our experience. In this series of cases, we have not observed the right axis deviation reported by Murnaghan, McGinn and White (16).

In spite of its limitations, the phlebogram yields information which is important in the control of thrombosis and embolism. Early detection of intravascular clotting by phlebography permits prompt institution of appropriate treatment, thereby preventing the occurrence or repetition of pulmonary embolism.

After thrombosis has occurred, rest, immobilization, and elevation of the extremity, and local heat, in many instances are inadequate in preventing embolism. More positive approaches such as administration of anticoagulants, or ligation of the vein proximal to the thrombus have been recommended (7–4–11). During the past several years numerous publications have appeared supporting the efficacy of proximal venous ligation in the prophylaxis of pulmonary embolism. Ligation of the femoral, common iliac and in some instances the vena cava proximal to the site of thrombosis has been carried out with lifesaving results and few adverse sequelae. The prophylactic and therapeutic use of anticoagulants in thrombosis and embolism has been reported by Wright (22), Bauer (2–3), Allen (1), Crafoord (5–6), Murray (17), Ravdin (19), Evans (9), and others. When the phlebogram reveals the presence of incipient thrombosis, early administration of substances which delay coagulation of the blood will abort the process, prevent extension of the thrombus, and diminish the hazard of embolism. If pulmonary embolism has already occurred, anticoagulant therapy will theoretically inhibit propagation of the clot into the lung and prevent a recurrence of embolism. The mode of action, dosage, methods of administration, advantages and disadvantages of the anticoagulants (5), Heparin and Dicumarol, have been discussed in detail in a previous communication (18). During the past 15 months Dicumarol alone and in combination with Heparin has been used at Walter Reed General Hospital in the treatment of thrombosis and embolism. Heparin was administered by constant intravenous drip, the dose being ad-

justed so as to maintain coagulation time between 15 to 20 minutes. (Lee White two tube method.) Dicumarol in 200–300 milligram doses daily was administered simultaneously by the oral route for 2 or 3 successive days. As soon as prothrombin percentage had fallen to 50 per cent of normal, Heparin was discontinued. Subsequent doses of Dicumarol were administered at 48–72 hour intervals depending upon the prothrombin level. Anticoagulant therapy was maintained for a period of 12–14 days. To date we have treated 12 cases of pulmonary embolism and 26 cases of thrombophlebitis. None of the patients with thrombophlebitis developed pulmonary emboli. No recurrences were observed in patients with previous pulmonary embolism. Obviously evaluation of results with Dicumarol therapy in a much larger series is necessary before any conclusions as to its efficacy can be drawn. Fatal embolism despite Heparin and Dicumarol therapy has been reported. Heparin and Dicumarol are both potentially dangerous (18). Their use should be reserved to cases in whom unequivocal clinical evidence of thrombosis exists or in whom suspected thrombosis has been confirmed by phlebography.

SUMMARY AND CONCLUSIONS

Ten cases are reported in which acute chest conditions are thought to have been caused by pulmonary embolism, with or without infarction, or with incomplete infarction, from various venous sources.

The patients were at work, had no cardiac disease and gave no history of known phlebitis. A possible exception may be noted in Case 8, in which a thrombosing hemorrhoid was noted at the time of the acute chest episode. None had been in bed and none had had a recent operation. In no case was the patient admitted with a correct diagnosis.

Phlebograms, roentgenograms and electrocardiograms are helpful in diagnosis. Criteria for interpretation of such laboratory findings have been recorded. Such tests should be employed when a relatively dry area of consolidation is found in the lungs without specific bacteriologic findings, and in which dyspnea or chest pain is an important symptom. The onset (as in cases 1 and 4) may be insidious or it may closely simulate coronary occlusion, pneumonia, angina pectoris, pericardial effusion etc.; in Case 4 the roentgenogram resembled that

of metastatic carcinoma. Cases of *repeated* "pleurisy" or "pneumonia," especially if bilateral, should be suspected of being due to pulmonary embolism. Probable sources of emboli have been found in leg veins, pelvic veins, thrombosing hemorrhoidal veins and veins of the prostatic and peri-prostatic plexus. In certain cases the source may remain unidentified in spite of the use of all of the usual methods of examination.

To date, we have been content to use Heparin and Dicumarol anticoagulant therapy, plus rest and elevation of the part affected by thrombosis or phlebitis. We have observed no detectable embolism after institution of such treatment.

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FURTHER OBSERVATION ON THE TREATMENT OF YAWS WITH PENICILLIN

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In a previous communication (1), we reported the effectiveness of penicillin in bringing about the healing of the cutaneous lesions of seventeen patients with primary or secondary yaws. In the present report, we wish to present further observations on this group of patients and, in addition, to summarize our findings in another twenty-five patients with yaws who were treated with penicillin. In the literature available to us since our first report, we have found no reference to the subject.

MATERIAL

Of the forty-two patients treated, five had primary yaws, thirty-six had secondary yaws and one had tertiary yaws. Nine patients had been treated previously with an arsenic or bismuth compound; thirty-three patients had received no specific therapy prior to hospitalization. The diagnosis of yaws was established in the forty-one patients with the primary or secondary form of the disease by the finding of spirochaetes morphologically identical with *Treponema pertenue* in the characteristic cutaneous lesions before treatment and by the presence of a positive serum Kahn reaction (2) at some time during the period of observation. The diagnosis of tertiary yaws in case #42 rests upon the data noted in the case report which follows.

All patients were hospitalized during the period of treatment with penicillin and were not discharged from the hospital wards until their lesions had healed. Penicillin dissolved in normal saline to make a final concentration of 10,000 units per cc. was administered intramuscularly in doses of 1.5 cc. to 3 cc. at three or four hourly intervals during the day and night until the arbitrarily selected total dose had been given. The potency of the penicillin used was ascertained by the method described in the previous communication (1). Groups of patients with primary or secondary yaws were treated with different total amounts of penicillin to determine whether or not the course of healing might be altered by varying the intensity of therapy. Eleven

patients received a total of 100,000 units of penicillin, sixteen patients between 250,000 units and 500,000 units, ten patients 1,200,000 units and four patients 2,400,000 units.

RESULTS

The accompanying tables summarize the results obtained in the treatment with penicillin of forty-two cases of yaws. In forty-one patients, lesions were shown by darkfield examination to contain spirochaetes morphologically identical with *T. pertenue* before treatment. In the lesions of all but three of these patients, no spirochaetes could be found sixteen hours after the institution of penicillin therapy. In these three cases, darkfield examination revealed no *T. pertenue* forty hours following the start of treatment. In every instance, the absence of spirochaetes from the lesions was confirmed by darkfield examination twenty-four hours after their initial disappearance. In no case was there any evidence of a Herxheimer-type reaction, a finding which differs from the experience of those treating early syphilis. In patients with early syphilis, febrile reactions have been noted to occur commonly after the institution of treatment with penicillin (3, 4). No toxic reactions were observed following the administration of penicillin to patients with yaws.

No difference in the rapidity of healing of primary and secondary cutaneous yaws was observed with the different schedules of treatment employed. In thirty-seven cases, healing was complete within three weeks of the beginning of therapy (Figures 1–6). In four cases (#10, #28, #30, #35), a single lesion located on the foot or ankle required four to eight weeks to heal (Figures 7–8). The slower healing of lesions in these locations suggests that trauma and increased venous pressure may have been factors associated with the delay.

All of the patients remained well following treatment with the single exception of case #1 whose course is described briefly.

Case No. 1—Fijian female, age ten years. Admitted 19 April 1944.

A ten year old Fijian girl was admitted complaining of sores on her legs. Her primary lesion had appeared three months previously and was followed a month later by the development of secondary yaws. At the latter time she had received one injection of an arsenical from which she derived only temporary benefit.

FIG. 1. CASE #19—SECONDARY YAWS BEFORE TREATMENT

FIG. 2. Case #19—Secondary yaws. Healed Mucocutaneous lesion eight days after start of treatment with 100,000 units of penicillin.

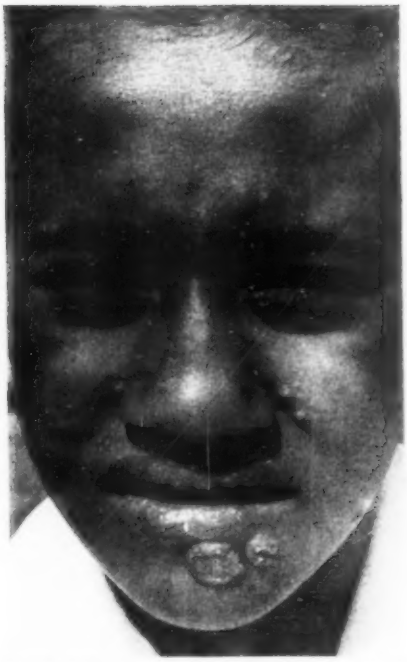

FIG. 3. CASE #27—SECONDARY YAWS BEFORE TREATMENT

FIG. 4. Case #27—Secondary yaws. Healed lesions with pigmented scars fourteen days after start of treatment with 1,200,000 units of penicillin.

FIG. 5. CASE #29—SECONDARY YAWS BEFORE TREATMENT

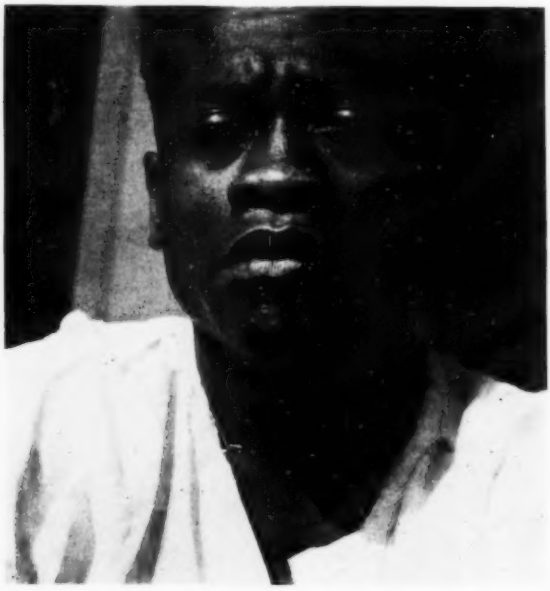

FIG. 6. Case #29—Secondary yaws. Healed lesions ten days after start of treatment with 2,400,000 units of penicillin.

FIG. 7. CASE #30—SECONDARY YAWS AND TINEA IMBRICATA BEFORE TREATMENT

FIG. 8. Case #30—Secondary yaws and tinea imbricata. The yaws have healed four weeks after start of treatment with 2,400,000 units of penicillin. The tinea imbricata has been unaffected.

Physical examination revealed a thin Fijian female with typical secondary yaws, lesions being present over each patella and on the right third finger. There was enlargement of the femoral lymph nodes bilaterally and of the right axillary glands. Darkfield examination of material from the lesion over the right patella showed numerous spirochaetes morphologically identical with *T. pertenue*. The serum Kahn reaction was negative.

Initially, the patient was given 25,000 units of penicillin intravenously. Thereafter, at four hourly intervals she received 15,000 units of penicillin intramuscularly until 190,000 units had been administered. Sixteen hours after the start of therapy, darkfield examination of material from the lesion on the right knee revealed no spirochaetes and this finding was confirmed at forty hours. A week after the first injection of penicillin, the lesions on the left knee and right third finger had healed completely and the lesion on the right knee had improved markedly. Darkfield examination of material from the small unepithelialized zone over the right patella was negative at this time. Because of the slower healing of this one lesion, the patient was given an additional 90,000 units of penicillin. She was discharged from the hospital essentially well, a small, thin eschar persisting on the right knee.

The patient's serum Kahn reaction, determined at weekly intervals, remained negative until 31 May 1944, at which time it became weakly positive, having a titre of 4 units. This finding was repeated the following week when the patient's skin was free of lesions. On 21 June 1944, a small eschar was noted at the site of the former lesion on the right knee. A week later, spirochaetes morphologically identical with *T. pertenue* were demonstrated in material obtained from beneath the eschar and the titre of the serum Kahn reaction was 80 units. The patient was hospitalized again and given 30,000 units of penicillin intramuscularly every three hours until 1,200,000 units had been administered. Spirochaetes could not be found in material from the lesion on the right knee after sixteen hours of treatment. Two weeks after admission, the lesion was healed completely and three weeks after admission, the serum Kahn reaction was negative. The patient was discharged from the hospital and not seen again for six weeks. At this time she appeared completely well. Her serum Kahn reaction, how-

ever, was again positive, titre 40 units. Whether or not this laboratory finding is indicative of another impending clinical relapse cannot be stated with certainty. Serologic relapses were observed in nine other patients without concomitant clinical relapse. It is hoped that further observations will provide an answer to this question.

In addition to the forty-one cases of primary or secondary yaws treated with penicillin, one case of tertiary yaws was treated with the drug. Because of the complexity of the case, the history is reported here in some detail.

Case No. 42—Half European-half Rotuman male, age fifteen years. Admitted 18 May 1944.

A fifteen year old half-caste male was admitted complaining of persistent cutaneous ulcers.

The patient's father (European) was said to have had yaws eighteen years previously. He denied having had syphilis and his serum Kahn reaction was negative. No history suggesting maternal syphilis was obtained. A brother had had yaws which had healed after treatment with an arsenical compound.

The patient's general health had been excellent prior to the onset of his present illness. The system review was not remarkable. The patient had lived in Rotuma all of his life except for short visits in Fiji.

The patient was quite well until early in 1939, when he was struck on the left wrist with a cricket ball. A swelling developed at the site of the injury which ulcerated two weeks later. The ulcer increased gradually in size and involved a considerable area on the left forearm. Thereafter, at varying intervals during the next five years, cutaneous swellings which ulcerated and healed very slowly or not at all appeared on the patient's extremities and less frequently on his trunk. In October, 1939, his serum Kahn reaction was positive. During the course of his illness, he was hospitalized several times for long periods and treated intensively with arsenic and bismuth compounds and with potassium iodide. At no time after the onset of his illness were all of his cutaneous lesions healed and on several occasions, new ulcerations appeared while the patient was receiving treatment. Those lesions which healed scarred deeply. Six months before his present admission, the patient developed painful swellings above his right wrist and below his left knee. These lesions did not ulcerate and remained

TABLE I

CASE NO.	AGE	SEX	RACE	TYPE OF YAWS	DURATION OF ILLNESS	SEVERITY OF ILLNESS	PREVIOUS THERAPY	INTERVAL BETWEEN PREVIOUS TREATMENT AND PRESENT ADM.	SERUM KAHN	DARKFIELD BEFORE TREATMENT	DARKFIELD AFTER 16 HRS. OF PENICILLIN TREATMENT	TOTAL PENICILLIN ADMINISTERED	TIME REQUIRED FOR HEALING OF LESIONS AFTER START OF PENICILLIN THERAPY	PERIOD OF OBSERVATION
												units		
1	10	F	Fijian	Secondary	3 months	Moderate	1 arsenic injection	1 month	Neg.	Pos.	Neg.	280,000	3 weeks	
				Secondary Relapse	5 months	Mild			Pos.	Pos.	Neg.	1,200,000	2 weeks	20 weeks
2	15	M	Fijian	Secondary	1 year	Moderate	None		Pos.	Pos.	Neg.	470,000	1 week	20 weeks
3	9	F	½-Fijian ½-Chinese	Secondary	1 year	Severe	3 arsenic injections	1 month	Pos.	Pos.	Neg.	510,000	8 days	19 weeks
4	12	F	Fijian	Secondary "Crab"	6 months	Moderate	3 arsenic injections	4 months	Pos.	Pos.	Neg.	480,000	2 weeks	18 weeks
5	1	F	Fijian	Secondary	3 months	Severe	None		Pos.	Pos.	Neg.	420,000	2 weeks	19 weeks
6	1	F	Fijian	Secondary	1 month	Severe	None		Pos.	Pos.	Neg.	420,000	11 days	3 weeks
7	9	F	Fijian	Secondary	1 year	Moderate	3 arsenic injections	1 month	Pos.	Pos.	Neg.	200,000	1 week	7 weeks
8	3	F	Fijian	Secondary	7 months	Mild	3 arsenic injections	5 months	Pos.	Pos	Neg.	525,000	9 days	17 weeks
9	4½	F	Fijian	Primary	1 week	Mild	None		Pos.	Pos.	Neg.	480,000	3 weeks	16 weeks
10	3	F	Fijian	Secondary	1 month	Moderate	None		Pos.	Pos.	Neg.	540,000	8 weeks	16 weeks
11	4	M	Fijian	Secondary	1 month	Moderate	None		Pos.	Pos.	Neg.	540,000	9 days	15 weeks
12	7	M	Fijian	Secondary	3 months	Moderate	None		Pos.	Pos.	Neg.	540,000	3 weeks	15 weeks
13	5	M	Fijian	Secondary	4 months	Severe	2 bismuth injections	2 months	Pos.	Pos.	Neg.	450,000	11 days	14 weeks
14	6	M	Fijian	Secondary	1 year	Moderate	None		Pos.	Pos.	Neg.	450,000	17 days	14 weeks
15	9	F	½-European ½-Samoan	Primary	3 weeks	Mild	None		Pos.	Pos.	Neg.	450,000	1 week	14 weeks
16	17	M	Fijian	Secondary	1 month	Severe	None		Pos.	Pos.	Neg.	450,000	10 days	10 weeks
17	1	M	Fijian	Secondary	2 months	Severe	None		Pos.	Pos.	Pos. Neg. after 40 hours	100,000	11 days	4 weeks

18	4	F	Fijian	Secondary	1 month	Moderate	None		Pos.	Pos.	Neg.	100,000	2 weeks	2 weeks
19	9	M	Fijian	Secondary	2 months	Moderate	None		Pos.	Pos.	Neg.	1,210,000	2 weeks	10 weeks
20	1	F	Fijian	Secondary	1 month	Moderate	None		Pos.	Pos.	Pos. Neg. after 40 hours	1,270,000	2 weeks	10 weeks
21	12	M	Fijian	Secondary	2 months	Moderate	None		Pos.	Pos.	Neg.	1,320,000	9 days	12 days
22	7	M	Fijian	Secondary	4 months	Moderate	None		Pos.	Pos.	Neg.	1,350,000	2 weeks	9 weeks
23	6	F	Fijian	Primary	1 month	Mild	None		Pos.	Pos.	Neg.	1,200,000	3 weeks	8 weeks
24	23	M	New Hebridesian	Secondary	2 months	Mild	None		Pos.	Pos.	Neg.	1,200,000	10 days	8 weeks
25	10	M	Fijian	Secondary	11 months	Mild	5 arsenic injections	9 months	Pos.	Pos.	Neg.	1,200,000	3 weeks	9 weeks
26	7	M	Fijian	Secondary	1 month	Mild	None		Pos.	Pos.	Neg	1,200,000	9 days	7 weeks
27	13	M	Fijian	Secondary	5 months	Severe	None		Pos.	Pos.	Neg.	1,200,000	2 weeks	8 weeks
28	5	M	Fijian	Secondary	1 month	Moderate	None		Pos.	Pos.	Neg.	1,200,000	4 weeks	7 weeks
29	17	M	Fijian	Secondary	2 months	Mild	None		Pos.	Pos.	Neg.	2,400,000	3 weeks	6 weeks
30	10	F	½-Fijian ½-Solomon	Secondary	3 months	Severe	None		Pos.	Pos.	Neg.	2,400,000	4 weeks	6 weeks
31	15	F	½-Fijian ½-Solomon	Primary	2 weeks	Mild	None		Pos.	Pos.	Neg.	2,400,000	10 days	7 weeks
32	5	M	Fijian	Secondary	1 month	Mild	None		Pos.	Pos.	Neg.	2,400,000	9 days	4 weeks
33	2	F	Fijian	Secondary	3 months	Severe	None		Pos.	Pos.	Neg.	100,000	3 weeks	3 weeks
34	13	M	Solomon	Secondary	1 month	Severe	None		Pos.	Pos.	Neg.	100,000	11 days	3 weeks
35	14	M	Fijian	Secondary	1 month	Mild	None		Pos.	Pos.	Neg.	100,000	4 weeks	4 weeks
36	2	F	Fijian	Secondary	3 months	Severe	None		Pos.	Pos.	Neg.	100,000	8 days	2 weeks
37	7	F	New Hebridesian	Secondary	3 months	Severe	None		Pos.	Pos.	Neg.	100,000	2 weeks	2 weeks
38	1	F	Hew Hebridesian	Secondary	1 month	Moderate	None		Pos.	Pos.	Neg.	100,000	11 days	2 weeks
39	6	F	½-Fijian ½-Solomon	Secondary	2 months	Severe	None		Pos.	Pos.	Neg.	100,000	11 days	11 days
40	2	F	Solomon	Secondary	8 months	Severe	1 arsenic injections	8 months	Pos.	Pos.	Neg.	100,000	11 days	11 days
41	12	M	Fijian	Primary	2 months	Mild	None		Pos.	Pos.	Pos. Neg. after 40 hours	100,000	2 weeks	2 weeks
42	15	M	½-European ½-Rotuman	Tertiary	5 years	Severe	See text		Neg.	Neg.		3,420,000	2 months	15 weeks

TABLE II

CASE NO.	BEFORE TREATMENT	1 WK.	2 WKS.	3 WKS.	4 WKS.	5 WKS.	6 WKS.	7 WKS.	8 WKS.	9 WKS.	10 WKS.	11 WKS.	12 WKS.	13 WKS.	14 WKS.	15 WKS.	16 WKS.	17 WKS.	18 WKS.	19 WKS.	20 WKS.	21 WKS.	22 WKS.	23 WKS.	24 WKS.
1	Neg.	Neg.		Neg.	Neg.	Neg.	Pos. 4 units	Pos 4 units		Pos. 4 units	Pos. 80 units		Pos. 20 units	Neg.							Pos. 40 units				
2	Pos. 12 units	Neg.	Pos. 20 units		Pos. 80 units	Pos. 80 units	Pos. 80 units		Pos. 80 units		Pos. 40 units		Pos 4 units	Pos. 40 units	Pos. 80 units	Pos. 40 units	Pos. 4 units	Pos. 40 units	Neg.	Pos. 4 units	Pos. 20 units				
3	Pos. 120 units	Pos. 120 units	Pos. 160 units	Pos. 240 units	Pos. 120 units	Pos. 200 units				Pos. 80 units		Pos. 160 units			Pos. 120 units		Pos. 160 units	Pos. 200 units	Pos. 120 units						
4	Pos. 20 units		Neg.	Neg.		Pos. 240 units	Pos. 240 units		Pos. 40 units	Pos. 120 units		Pos. 80 units		Pos. 80 units	Pos. 80 units		Pos. 200 units								
5	Pos. 4 plus	Pos. 240 units	Pos. 320 units		Pos. 200 units		Pos. 120 units							Pos. 80 units		Pos. 120 units	Pos. 20 units	Pos. 40 units							
6	Pos. 4 plus	Pos. 160 units	Pos. 200 units	Pos. 200 units																					
7	Pos. 4 plus	Pos. 240 units	Pos. 200 units	Pos. 240 units	Pos. 200 units		Pos. 200 units																		
8	Pos. 2 plus	Pos. 80 units			Pos. 4 units		Pos. 80 units	Pos. 4 units		Pos. 80 units				Pos. 4 units	Pos. 4 units	Pos. 20 units	Pos. 40 units	Pos. 40 units							
9	Pos. 120 units	Pos. 160 units	Pos. 40 units	Pos. 40 units			Pos. 40 units		Pos. 80 units		Pos. 80 units		Pos. 20 units		Pos. 160 units		Pos. 80 units								
10	Pos. 80 units	Pos. 200 units	Pos. 240 units	Pos. 200 units		Pos. 200 units		Pos. 160 units		Pos. 4 units	Pos. 40 units	Pos. 20 units					Pos. 80 units								

| | | |

TABLE II—*Continued*

CASE NO.	BEFORE TREATMENT	1 WK.	2 WKS.	3 WKS.	4 WKS.	5 WKS.	6 WKS.	7 WKS.	8 WKS.	9 WKS.	10 WKS.	11 WKS.	12 WKS.	13 WKS.	14 WKS.	15 WKS.	16 WKS.	17 WKS.	18 WKS.	19 WKS.	20 WKS.	21 WKS.	22 WKS.	23 WKS.	24 WKS.
23	Pos. 240 units	Pos. 20 units	Pos. 4 units	Pos. 20 units	Pos. 4 units		Pos. 20 units		Pos. 4 units																
24	Pos. 240 units	Pos. 80 units	Pos. 4 units		Pos. 4 units		Pos. 4 units		Pos. 4 units																
25	Pos. 240 units	Pos. 240 units	Pos. 40 units	Pos. 240 units	Pos. 240 units		Pos. 240 units			Pos. 240 units															
26	Pos. 240 units	Pos. 160 units	Pos. 160 units	Pos. 200 units	Pos. 200 units	Pos. 120 units		Pos. 120 units																	
27	Pos. 240 units	Pos. 240 units	Pos. 200 units	Pos.	Pos. 160 units		Pos. 40 units	Pos. 40 units																	
28	Pos. 40 units	Pos. 40 units	Pos. 4 units	Neg.		Pos. 4 units		Pos. 4 units																	
29	Pos. 240 units	Pos. 120 units	Pos.	Pos. 160 units			Pos. 120 units																		
30	Pos. 240 units	Pos. 240 units	Pos. 200 units	Pos. 240 units	Pos. 240 units		Pos. 240 units																		
31	Pos. 80 units	Neg.	Pos. 40 units	Pos. 160 units	Pos. 120 units			Pos. 120 units																	
32	Pos. 240 units	Pos. 240 units	Pos. 160 units		Pos. 80 units																				

| | | |

more or less unchanged until the patient was hospitalized on this occasion. The ulcerative lesions present at the time of this admission had been noted first early in 1943.

Physical examination revealed a well developed, fairly well nourished half-caste male who did not appear ill. He was afebrile. The skin was light brown and of soft, smooth texture. On the dorso-medial aspect of the left foot, there were four discrete granulomatous lesions in close approximation to one another. These lesions, each one to two centimeters in diameter, had sharp, slightly rolled, pearly grey margins. The central portion was composed of strawberry-red, exuberant granulations which were covered with a thin seropurulent discharge. There was a similar lesion over the medial malleolus of each ankle, one over the right Achilles tendon and one over the medial epicondyle of the right humerus. There were numerous scars of previously healed lesions distributed over the extremities and to a lesser degree over the trunk. These were deep-seated scars such as might follow a severe burn. The most extensive scar involved the left wrist where there was considerable atrophy of the subcutaneous tissues with a resultant partial flexion contracture of the joint. Over the right tibial tubercle and over the lower third of the right ulna, there were warm, tender, slightly erythematous swellings. The adjacent joints were not involved in the inflammatory process. No glandular enlargement was noted. The pupils were equal and reacted normally. The optic fundi were normal. The nasal septum was intact. There were no Hutchinson's teeth. The heart and lungs were not remarkable. B.P. 122/80. The tip of the spleen was felt readily on inspiration. Neurological examination was normal.

Laboratory studies revealed the following data: RBC: 5,000,000/cu. mm. Hgb.: 11.4 Gm. WBC: 11,000/cu. mm. Differential WBC: PMN 67%, Lymph 23%, Mono 10%. Serum Kahn reaction: negative on admission, positive after 10 July 1944 (see Table II). Total serum protein: 7 Gm%. A/G: 2.3. B.U.N.: 18 mgm.%. Spinal fluid: clear, 6 WBC/cu. mm., Pandy negative, Kahn reaction negative. Urine: yellow, sp. gr. 1.028, sugar absent, albumen 2 plus, microscopic examination revealed many RBC. PSP: 48% in 2 hours. Stool examination: no ova or parasites. Examinations of material from the ulcers on the left foot revealed no spirochaetes, tubercle

bacilli, fungi, aerobic or anaerobic pathogens (Staph. albus cultured). Biopsy showed granulation tissue with marked lymphocytic infiltration and moderate numbers of plasma cells and eosinophils. An occasional giant cell was present. Biopsy of the periosteum of the right tibia showed granulation tissue in which many plasma cells were present. X-rays of the long bones showed lesions compatible with those of tertiary yaws in the left fibula, in both tibiae and in the right ulna. The x-ray of the right ulna (figure 9) revealed an area of

FIG. 9. Case #42—X-ray of right ulna 25 May 1944. There is an area of bony destruction 4 cms. above the wrist joint accompanied by marked periosteal proliferation.

bony destruction 4 cms. above the wrist joint accompanied by marked periosteal proliferation. X-rays of the chest and intravenous pyelograms were within the limits of normal.

FIG. 10. Case #42—X-ray of right ulna 4 August 1944. There is extensive bony repair and replacement at the site of the lesion described previously. There appears to be healing periostitis.

Because the patient's lesions had proved refractory to the drugs employed ordinarily in the treatment of yaws, it was decided to treat him with penicillin. Treatment with 90,000 units of penicillin intramuscularly per day was started on 8 June 1944, and continued until

the patient received a total of 1,020,000 units. Following the institution of this form of therapy, the patient noted immediate subjective improvement. In several days, beginning epithelialization of the cutaneous lesions was in evidence and, thereafter, healing progressed slowly but steadily. The tenderness of the right tibia and right ulna disappeared a week after the start of treatment with penicillin. Hematuria, noted on admission, subsided rapidly and disappeared after four weeks of treatment and the patient's excretion of PSP in two hours rose to 84%. The spleen decreased in size but the tip remained just palpable. On 10 July 1944, the serum Kahn reaction was found to be positive, titre 240 units, despite continued clinical improvement. Because of this finding and the pronounced chronicity of the patient's illness, he was given another 2,400,000 units of penicillin. On 14 August 1944, all of the patient's cutaneous lesions were healed for the first time since his illness had begun. Repeat x-ray films of the long bones showed evidence of extensive bony repair, especially in the right ulna (figure 10) and left fibula. The patient's serum Kahn reaction was still positive, titre 240 units, twelve weeks after the start of treatment. At this time, his skin lesions were still completely healed.

In this group of patients, penicillin was ineffective in altering the course of scabies, tinea imbricata, and molluscum contagiousum. It did not affect intestinal infestations with hookworm, *Entamoeba histolytica*, and *Ascaris lumbricoides*.

DISCUSSION

The extension of the original observations provides added evidence that penicillin is an effective agent in bringing about the healing of the cutaneous manifestations of primary and secondary yaws. The schedule of treatment was altered several times in an effort to determine a reasonably effective amount of penicillin that might be utilized for the mass therapy of yaws. The period of observation was not sufficiently prolonged to provide adequate information concerning the rate of relapse accompanying any of the schedules employed. In this group of patients, there was only one clinical relapse in the forty-one cases with primary or secondary yaws observed for periods as long as twenty weeks following the institution of penicillin therapy. When it was found that the lesions of thirteen patients treated with 100,000

units of the drug (cases #19 and #20 were treated originally with this amount and were given additional penicillin when clinically well following the relapse of case #1) healed as rapidly as those of patients treated with larger quantities of penicillin, it was felt this total dose was the one that should be subjected to further clinical trial. A schedule of treatment calling for four intramuscular injections of 25,000 units of penicillin at three or four hourly intervals would require hospitalization for only one day and might be utilized without prohibitive difficulty in the treatment of large numbers of patients in the field. If the dose of 100,000 units of penicillin continues to show consistent curative properties and is followed by a low rate of relapse, its employment in mass therapy would be a safe and practical method for the elimination of yaws from a community. The Jamaica Yaws Commission (5) found that this end could be accomplished by the treatment with six weekly injections of neoarsphenamine of persons infected with yaws and by a "follow-up" at four to eight months with further treatment of cases that relapsed. A similar program might be carried out employing penicillin. Penicillin produces almost no toxic reactions, and, in the suggested dose, it can be administered in a shorter period of time than is necessary for the recommended amount of arsenical. From the data of Mahoney et al. (3) and of Moore et al. (4), it is apparent that early syphilis treated with amounts of penicillin as large as 1,200,000 units is followed by a significant rate of relapse. Moore and his co-workers found that the rate of relapse of early syphilis treated with penicillin varied inversely with the amount of drug employed and directly with the duration of the disease. They noted also that the disappearance of spirochaetes from surface lesions and the healing of the lesions occurred with equal rapidity whether total doses of 60,000 units or of 1,2000 units of penicillin were employed. Marked differences exist, however, between both the etiologic agents and the clinical courses of yaws and syphilis and it is possible that the former disease can be controlled by much smaller amounts of penicillin than seem necessary for the treatment of syphilis. The Jamaica Yaws Commission (5) stated that one third of all cases of yaws treated with six weekly injections of neoarsphenamine relapsed within two and one half years. Whether or not treatment of yaws with 100,000 units of penicillin in one day will be followed by an ap-

preciably greater rate of relapse is a problem requiring further study. Because of a change in station, the authors were obliged to discontinue active participation in this investigation. Further observations on the immediate and late results of the treatment of primary and secondary yaws with 100,000 units of penicillin are being conducted at the Colonial War Memorial Hospital, Suva, Fiji.

The effect of penicillin in a single case of tertiary yaws has been described. The patient, who had proved refractory to therapy with arsenic and bismuth compounds and with potassium iodide, responded very satisfactorily to the administration of penicillin. It may be that penicillin will prove a valuable adjunct in the treatment of early and late lesions of yaws which are resistant to therapy with heavy metals. This problem also merits further study.

Since the writing of the original report (1), additional quantitative serum Kahn tests (table II) have been carried out. There was a tendency in some cases for the titre of the serum Kahn reaction to decrease with time, but in no case was there permanent reversal to negativity. In ten patients, serologic relapses were observed at different times following treatment with penicillin but in only one case was this finding followed by a clinical relapse. The variations in the titre of the serum Kahn reaction of some patients and the failure of any patients to develop persistently negative Kahn reactions are unexplained findings. The Jamaica Yaws Commission (5) found that the Wassermann reaction became negative in a third of their cases six months after treatment with six weekly injections of neoarsphenamine. Several authors (6, 7) emphasize, however, the difficulty in producing negative blood serologic tests in yaws despite therapy with arsenic or bismuth compounds sufficient to effect healing of the cutaneous lesions. The serologic study of our group of patients is being continued at the Colonial War Memorial Hospital.

CONCLUSIONS

1. Penicillin brought about the rapid and complete healing of the cutaneous lesions of forty-one cases of primary and secondary yaws.

2. There was one clinical relapse which responded well to retreatment in this group of patients observed for periods as long as twenty weeks following the institution of therapy.

3. Penicillin was used successfully in the treatment of one case of tertiary yaws which had proved previously refractory to therapy with arsenic and bismuth compounds and with potassium iodide.

4. During the period of observation penicillin did not effect permanent seronegativity in any of the forty-two cases of yaws treated.

5. The use of 100,000 units of penicillin administered within twelve hours merits further study because of its potential value in the mass treatment of infectious yaws.

The authors wish again to express their appreciation to Mr. J. Eric Pery-Johnson and to the medical and nursing staffs of the Colonial War Memorial Hospital, Suva, Fiji, for their continued interest and cooperation in this study.

We are indebted to Major Harry M. Robinson, Jr., M.C., for the photographs used in figures 1 and 3 and to Sergeant Isacson, U. S. Army Signal Corps, for the photographs used in the remaining figures. Lieutenant Colonel Webster H. Brown, M.C., interpreted the x-ray films in case #42.

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THE ISOLATION OF THROMBOPLASTIN FROM LUNG TISSUE

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The term thromboplastic substance was introduced originally by Nolf to signify any agency, physical or chemical, which facilitates the clotting of blood but it is usually restricted to a special chemical substance, or possibly to a group of substances, furnished by the tissues or the blood, which has this property or characteristic. It has been called by many different names in physiological literature: zymoplastic substance, thrombokinase, cytozyme, thrombozyme, tissue fibrinogen, tissue coagulin, thromboplastin, etc. Each of these terms carries some special connotation, depending on the author's theory of coagulation, but they all refer to this substance present in the tissues which is concerned in the initiation of the process of clotting.

In the mammal we have thromboplastic substance furnished by the platelets of the blood and by the extravascular tissues in general. There is general agreement that the largest concentration is found in the lungs. The nature of this substance has been investigated by many workers without conclusive results.

Over a period of eight years the author carried on a series of experiments in which a great variety of methods were tried in an attempt to isolate and purify thromboplastin from lung tissue with two main objects in view: first, the development of a method for obtaining a usable preparation of thromboplastin, with possible practical applications such as the control of hemophilic bleeding, or as a hemostatic agent, or as a reagent in the determination of prothrombin times and

[1] The work reported here was carried out under a grant from the Carnegie Corporation and subsequently under a grant from the Rockefeller Foundation Fluid Research Fund of the Johns Hopkins University School of Medicine.

[2] This research was in progress at the time of Dr. Howell's death and this paper was prepared from his notes and from his most recent report of progress by Janet Howell Clark.

[3] On behalf of the author acknowledgement is here made to Mr. Jesse Yaffa for his loyal cooperation as technical assistant in these experiments.

second, the isolation of the thromboplastin in sufficient purity to determine its chemical nature.

METHOD

Material has been prepared from human and pig lungs which can be kept for a long time in dry form in sealed glass tubes, in CO_2 or, after sterilizing by heat, in alkaline solution in sterile serum tubes. In every experiment tests were made with hemophilic blood at each step of the procedure to follow the potency of the extracted material.

Although different variations in the procedure were being continually tested the method found most satisfactory involved the following steps:

1. An aqueous extract of minced lung tissue precipitated by acetic acid.
2. Treatment of an alkaline solution of the precipitate with Lloyd's reagent.
3. Precipitation of the supernatant liquid from 2 by trichloracetic acid.
4. Extraction of the precipitate with calcium malonate.
5. Repeated aqueous extracts of the material left after extraction with calcium malonate.
6. Precipitation of the aqueous extracts by trichloracetic acid.

These last precipitates were obtained by centrifuging and dried in thin layers. The waxy material obtained is soluble in faintly alkaline water and has a strong thromboplastic action, clotting hemophilic blood in one to two minutes in concentrations of 1 mgm. to 15 to 20 cc. of blood.

This material is not thromboplastin in pure form as analyses made on different samples show variable results. It will be referred to as the crude material in discussing the results below. The detailed procedure used to prepare it is as follows:

Fresh pig lung is cut into small pieces and run through a grinder. It is stirred 1 hour in 1500 cc. of water, pH 7.0, and then filtered through a large Buchner with suction. The filtrate is precipitated by adding 1 per cent acetic acid until a good precipitate forms. The material left in the Buchner is given a second extraction with 1500 cc. of water and the second filtrate is also precipitated with acetic acid.

The precipitates with 1 per cent acetic acid are centrifuged off promptly as keeping over night in acid solution weakens the activity. The centrifuged precipitate is washed by filling the tubes with distilled water, stirring and recentrifuging.

The washed precipitate is treated with 250 cc. of alkaline water N/100 NaOH, stirred well to break up lumps and the solution made faintly but distinctly alkaline to neutral paper by careful addition of N/10 NaOH. The mixture is allowed to stand for some hours (over night) in an ice box (10°–14°C.).

The solution is brought to room temperature while stirred with an electric stirrer and is then treated with Lloyd's reagent in the proportion of 0.5 grams to each 10 cc. The mixture is warmed to 40°C. and stirred at that temperature for 10 minutes. It is then centrifuged at 2000 r.p.m. for 30 minutes.

The supernatant turbid liquid is decanted into a beaker, filtered with suction and precipitated by adding, with stirring, a 5 per cent solution of trichloracetic acid until a distinct precipitate forms.

The precipitate is centrifuged off, the supernatant liquid is discarded and the precipitate is stirred for an hour in 200 cc. of a 0.1 per cent solution of calcium malonate (freshly prepared).

This mixture is centrifuged for 30 minutes at 2000 r.p.m., the supernatant liquid is discarded and the precipitates are extracted for four or five successive times with about 375 cc. of distilled water each time as follows:

Each extract is stirred for about 30 minutes, then centrifuged for 5 minutes at 2000 r.p.m. The supernatant liquid is decanted into a beaker and precipitated by careful addition of a 2.5 per cent solution of trichloracetic acid. The precipitate is collected by centrifuging each precipitate, as it is obtained, and is stirred in about 25 cc. of a N/1000 solution of NaOH, and sufficient of a N/10 solution of NaOH added to make the reaction faintly alkaline to neutral paper. The combined precipitates of the water extracts are well stirred in the alkaline solution until all lumps are dissolved and the mixture is kept over night in the ice box.

This solution is reprecipitated by adding a 2.5 per cent solution of trichloracetic acid. The precipitates are obtained by centrifuging, removed from the tubes with a spatula and spread thinly on large glass plates and dried as rapidly as possible before an electric fan (in warm dry air).

The dried material is scraped off promptly with a razor blade and sealed in glass tubes, in CO_2.

When needed the material is dissolved in N/1000 solution of NaOH, using 1 mgm. to 1 cc., and adding if necessary enough of a N/1000 solution of NaOH to make the solution just alkaline to neutral litmus paper. The material dissolves slowly on stirring and should be filtered if there is any visible insoluble residue.

This crude preparation contains protein and appears to be a protein compound of a phospholipid. Most of the recent experiments have been an attempt to separate off the phospholipid component and determine whether it exhibits thromboplastic activity. The unstable character of the compound when exposed to air or to chemical manipulation has limited the methods that can be used for this purpose. The most successful procedure so far developed is as follows:

The dry material is given two successive extractions with petroleum ether at 0°C. Experience has shown that some inhibitory substance or relation is removed by this extraction. There is also some loss of active substance, but not much at the temperature used. After this extraction the material is dried in a current of CO_2 and is then extracted with benzene at room temperature. The benzene extract, after centrifuging, is evaporated to dryness in a current of CO_2 and is extracted successively with cold acetone and cold alcohol. The remaining material, dried in CO_2, is dissolved in a small amount of chloroform which is centrifuged, filtered, concentrated by CO_2 and is then precipitated by a small excess of absolute alcohol. The material thus obtained is small in amount but very active. It still shows the presence of some protein to the buiret reaction. On microanalysis[4] it gives 4.09 per cent of nitrogen to 2.97 per cent of phosphorus—a ratio of 3 of nitrogen to 1 of phosphorus. To remove the protein the following procedure is used. The alcohol precipitate, after drying in CO_2, is dissolved in chloroform or benzene. Benzene was found more satisfactory than chloroform as the insoluble material is more readily separated. A portion is undissolved and can be obtained by centrifuging. This portion contains protein as shown by the buiret reaction, and has slight thromboplastic activity. The portion that goes into solution in the chloroform or benzene is obtained by evaporating the solution to dryness in a stream of CO_2, dissolving the residue in alkaline water and precipitation by trichloracetic acid. This portion is apparently free from protein and shows marked thromboplastic activity. The yield from a single lung is small, from 10 to 20 mgm. So far not enough of this material has been prepared to make a determination of its chemical nature.

Although most of the thromboplastin was prepared from pig lungs a series of preparations were made from human lungs with the hope of getting a substance that could be used for injection in hemophilia. It was found that drying on glass weakens the human material more than pig material, possibly on account of the carbon that is invariably present in the adult human lung. Also chloroform extracts the active material less perfectly in human preparations so that purification of the human material was not attempted and the material was prepared and kept in CO_2 or in serum tubes in the crude form only.

RESULTS

Stability of Material

Human lung material in sterile serum tubes was prepared as follows: Lloyd's reagent, trichloracetic acid, calcium malonate, precipitation

[4] This analysis was made through the courtesy of Dr. J. A. Leighty of the Lilly Research Laboratories.

by trichloracetic acid, the precipitate dissolved, reprecipitated and redissolved, heated in boiling water for 5 minutes, cooled and placed in sterile serum tubes.

Case	*Date prepared*	*Initial Activity*
H 52	10/22/42	<1.0 min.
H 53	12/15/42	2.0 min.
H 55	3/23/43	1.5 min.

On March 11, 1944 these tubes were combined, reboiled and tested. Activity = < 2 min. Human lung material prepared as above and kept dry in CO_2 tubes.

Case	*Initial Activity*	*Subsequent Activity*
H 6	50″	After 3 years 5 mos. 1.5′
H 15	1.0′	After 3 years 6 mos. <2.0′
H 16	1.5′	After 3 years 6 mos. <2.0′
H 20	<1.0′	After 3 years 6 mos. <2.0′
H 56	<1.0′	After 1 year 6½ mos. <1.0′

Pig lung material in which the trichloracetic acid precipitate was extracted with acetone, petroleum ether and chloroform and put up in sterile serum tubes showed little loss of activity in 2 years and 7 months in one case but some deterioration in others.

Pig lung material in which the trichloracetic acid precipitate was extracted with acetone, benzene, petroleum ether and chloroform, evaporated in air and the residue dissolved, precipitated by acid, dried and put up in CO_2 tubes showed practically no deterioration in three and a half years in two preparations.

Results of intravenous injection of crude thromboplastin

Pig thromboplastin: Through the kindness of Dr. Hogan of the University of Missouri some of the material prepared from pig lungs was tried intravenously on his unique strain of hemophilic pigs. This material was prepared by the method giving the crude thromboplastin and was put up in sterile serum tubes. The results were interesting and suggestive. The pigs showed no unfavorable reactions. The clotting time was reduced for a period of at least four hours. After 12 hours the blood returned to its usual clotting time, but after an interval of 48 to 72 hours there was again a marked and continuing reduction in clotting time.

This latter reaction was unexpected. The experiments will be re-

ported in detail by Dr. Hogan and his co-worker Dr. Muhrer. Dr. Hogan hopes within a short time to continue the observations with especial reference to the delayed effect.

Human thromboplastin: Through the courtesy of Dr. Philip Wagley of the Johns Hopkins Hospital the combined human material from H 52, H 53 and H 55 was injected intravenously in a human case—a woman who was bleeding profusely as a result of aplastic anemia. The patient received two injections of 10 cc. each, six days apart. The only untoward response was a chill 45 minutes after the first injection. A rise in temperature briefly to 104.2° followed the second injection but this may have been due to a blood transfusion. The patient seemed favorably affected. Bleeding from the gums, pharynx and nose ceased. Coagulation time before the first injection was 28 minutes, six days after the first injection it was 14 minutes and ten days after the second injection it was 8.5 minutes. Plasma fibrinogen increased 50 per cent.[5] Twelve transfusions of 500 cc. each were given during the three weeks prior to the administration of thromboplastin and during the following three weeks six transfusions of 500 cc. each maintained the same hemoglobin level. There was no evidence of blood regeneration. Three days before death (10 days after the last injection) an intracutaneous test of 0.1 cc. of lung extract caused itching and a suggestion of wheal formation so that no further treatment was given.

CONCLUSION

Although the isolation of thromboplastin in sufficient purity to determine its chemical nature was not successfully completed it was evident that the crude material is a protein compound of a phospholipid. A method for preparation of this crude material has been perfected which gives a substance with strong thromboplastic action capable of clotting hemophilic blood in one to two minutes in concentrations of 1 mgm. to 15 or 20 cc. of blood. This material can be kept in dry form in CO_2 with practically no loss of potency and, after sterilizing by heat, in alkaline solution in sterile serum tubes with very slight loss of potency.

[5] Clinical notes are through the courtesy of Dr. Wagley who expects to give further details including fibrinogen determinations and prothrombin times in a subsequent report.

Material kept in liquid form in serum tubes has been used intravenously without unfavorable reactions, the pig material in a strain of hemophilic swine and the human material in a single clinical case. This gives a definite hope that material prepared in this form might be used to control hemophilic bleeding.

Further purification of this crude material showed that it was possible to remove the protein, leaving a residue with marked thromboplastic activity, the chemical nature of which has not been determined.

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Penicillin DOSAGE TABLE*

INDICATIONS	INITIAL DOSE (UNITS)	CONTINUING DOSAGE (UNITS)	UNITS IN 24 HR.	REMARKS
Serious Infections (staphylococcus, clostridium, hemolytic streptococcus, anaerobic streptococcus, pneumococcus, gonococcus, anthrax, meningococcus) Adults and children	15,000 to 20,000	(a) Intravenous drip: 2000 to 5000 every hr.	40,000 to 120,000 or more	(a) Dissolve ½ of 24 hr. dose in 1 liter (1000 cc.) normal saline; let drip at 30 to 40 drops per minute.
		or (b) Intramuscularly: 10,000 to 20,000 every 3 or 4 hr.	40,000 to 120,000 or more	(b) Concentration: 5000 U. per cc. normal saline.
		or (c) Intramuscular drip	40,000 to 120,000 or more	(c) Total daily dose in 250 cc. normal saline.
Infants	5000 to 10,000	3000 to 10,000 intramuscularly every 3 hr.	20,000 to 40,000 or more	Each dose in 1 or 2 cc. of normal saline.
Chronically infected compound injuries, osteomyelitis, etc. Adults and children	5000 to 10,000	10,000 every 2 hr. or 20,000 every 4 hr. intramuscularly or intravenously. Larger doses may be necessary at times.	40,000 to 120,000 or more	Concentration for intramuscular inj.: 5000 U. per cc. normal saline. For intravenous inj.: 1000 to 5000 U. per cc. Supplement with local treatment.
Gonorrhea	20,000 every 3 hr. intramuscularly for 5 doses		100,000	Results of treatment should be controlled by culture of exudate.
Empyema Adults and children	30,000 to 40,000 once or twice daily into empyema cavity		30,000 to 80,000	Dissolve in 20 to 40 cc. normal saline and inject into empyema cavity after aspiration of pus.
Meningitis Adults and children	10,000 once or twice daily into subarachnoid space or intracisternally		10,000 to 20,000	Concentration: 1000 U. per cc. normal saline.
Bacterial Endocarditis Adults and children	25,000 to 40,000	25,000 to 40,000 every 3 hr. intramuscularly	200,000 to 300,000	Continuous treatment for 3 weeks or longer. In a few cases the intravenous drip is more advantageous.

*Based upon recommendations by Chester S. Keefer, *War Production Board Penicillin Leaflet*, Apr. 1, 1945; and by Wallace E. Herrell and Roger L. J. Kennedy, *Journal of Pediatrics*, 25:505, Dec., 1944.

Write for pocket size copies of this Dosage Table

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